MODELING THE EPIDEMIOLOGIC AND ECONOMIC IMPACTS OF NOSOCOMIAL INFECTION PREVENTION STRATEGIES

by

Rachel Rubin Bailey

B.S., Tulane University, 2007

M.P.H., University of Pittsburgh, 2008

Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

by

Rachel Rubin Bailey

It was defended on

February 23, 2011

and approved by

Dissertation Advisor:
Bruce Y. Lee, MD, MBA
Assistant Professor
Departments of Epidemiology, Medicine, and Biomedical Informatics
Graduate School of Public Health and School of Medicine
University of Pittsburgh

Committee Member:
Maria M. Brooks, PhD
Associate Professor
Departments of Epidemiology and Biostatistics
Graduate School of Public Health
University of Pittsburgh

Lee H. Harrison, MD
Professor
Departments of Medicine, Infectious Diseases and Microbiology, and Epidemiology
School of Medicine and Graduate School of Public Health
University of Pittsburgh

Robert R. Muder, MD
Professor
Department of Medicine
School of Medicine
University of Pittsburgh

Ronald E. Voorhees, MD, MPH
Visiting Associate Professor
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

MODELING THE EPIDEMIOLOGIC AND ECONOMIC IMPACTS OF NOSOCOMIAL INFECTION PREVENTION STRATEGIES

Rachel Rubin Bailey, PhD

University of Pittsburgh, 2011

It is estimated that more than 1.7 million nosocomial infections and 98,000 deaths occur annually in the U.S. Nosocomial infections are associated with a longer length of stay (LOS), which is in-turn associated with higher costs and is a risk factor for additional infections. Infection prevention measures may allow a significant number of cases to be averted, although consensus has not been reached about the ultimate epidemiologic and economic value of prevention strategies. A multifaceted program of nosocomial infection prevention evaluating the surveillance test attributes, target population, and intervention implementation has potential to both improve patient outcomes and reduce healthcare costs. I developed models to evaluate and estimate the impact of these infection control interventions. First, testing adult hospital inpatients has the potential to prevent transmission of MRSA among patients. However, policy makers and hospital administrators must consider the diagnostic test used in a screening program. Increasing the number of anatomic sites tested with surveillance cultures does not appear to have as great an impact as decreasing turnaround time on the economic value of a MRSA testing strategy. Second, weekly surveillance of neonates in the neonatal intensive care unit (NICU) and isolation of those who test positive is a technique that hospitals could use to decrease the incidence on nosocomial infections, selecting neonates as a target population where MRSA infections have substantial morbidity. Hospitals with moderate to high adherence to isolation protocols have the potential to prevent adverse clinical outcomes and mortality among NICU populations. Third,

routine dispensing of home-based preoperative chlorhexidine bathing kits has the potential to prevent post-operative surgical site infections (SSIs). Our model suggests that preoperative bathing would have substantial economic value throughout a wide range of intervention implementation scenarios: patient compliance levels, cloth efficacies, costs, and SSI-attributable LOS, supporting the distribution of chlorhexidine cloths preoperatively. The public health significance is that decision makers can use the models described here to benchmark the test characteristics, potential target populations, and intervention implementation strategies to utilize in local infection prevention programs. A comprehensive approach including the interventions modeled here may help move towards the elimination of healthcare acquired infections.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

When I began infectious disease modeling I was an eager, although incredibly inexperienced, young researcher who was fascinated by infectious disease dynamics and prevention strategies. Dr. Bruce Lee, my committee chair, gave me the opportunity to learn about computational modeling and apply this exciting methodology to a broad spectrum of infectious disease projects. I have had opportunities to work on projects that I never would have dreamed of and learned so much along the way. I would like to thank the members of my dissertation committee, for their probing questions have truly allowed me think like a researcher and have vastly improved my research.

My friends and family also deserve thanks for their seemingly endless encouragement. My parents have always supported me in achieving whatever goals I have set for myself. They have moved me (and my shoes) from state to state in pursuit of my academic goals without complaint. My brothers, Josh and Ben, and sister, Leah, have also supported me in their own way always asking, “Will you ever be done with school?” I promise this is the last graduation ceremony they will have to sit through for me. Marshall, my fiancé, has been a great support throughout graduate school. He has always been there to listen to me talk about my projects and bring me cupcakes to cheer me up when projects have encountered challenges. He has helped me maintain balance throughout this whole process.

Finally, I would also like to acknowledge the Journal of Infection Control & Hospital Epidemiology for publishing the manuscript found in Section 4, “The Economic Value of Dispensing Home-Based Preoperative Chlorhexidine Bathing Cloths to Prevent Surgical Site Infections” and granting me permission to republish it as a part of my dissertation.

1.0 INTRODUCTION

Substantial preventable nosocomial infection attributable morbidity and mortality occur each year in the United States and globally.[1] It is estimated that more than 1.7 million nosocomial infections occur annually in U.S. hospitals with more than 98,000 nosocomial deaths per year.[2] Infections that are acquired during a patient's stay as a result of exposure to infection agents within a healthcare setting are classified as nosocomial infections. These infections were neither present nor known to be incubating on admission and can be either systemic or localized.[2] Nosocomial infections are often classified by anatomic site at which they occur or the causative agent of infection. Surgical site infections account for approximately 20% of all nosocomial infections in the United States.[2] According to the National Healthcare Safety Network (NHSN), the pooled mean number of central line associated bloodstream infections (CLABSI) in adult medical inpatient wards was 1.5 per 1,000 central line days.[3] Before 2005, NHSN was three distinct nosocomial infection surveillance systems: the National Nosocomial Infections System (NNIS), the Dialysis Surveillance Network (DSN) and National Surveillance System for Healthcare Workers (NaSH).[3]

Nosocomial infections are associated with a longer length of stay (LOS) in the hospital, which in turn is associated with higher costs and can be a risk factor for the occurrence of additional infections.[4] Nosocomial infections affect patients of all ages, from neonates to adult elective surgery patients, to older adults in long-term care facilities.[5-7] The emergence of

multidrug resistant organisms (MDROs) has brought increased attention to nosocomial infections due to the limited antibiotic treatment options.[5] The second and third line treatments for these infections often have lower efficacy, are more toxic resulting in side effects for patients, and tend to be much more expensive than first line antibiotic treatments.[8] In fact, the Centers for Disease Control and Prevention (CDC) reports that more than 70% of hospital-acquired bacterial infections are resistant to at least one of the most common drugs used to treat them.[8] Moreover, patients with MDRO infections may have delayed appropriate antibiotic treatment, increasing patient morbidity and healthcare costs.[9] Delayed treatment has also been established as an independent predictor of infection-related mortality.[10]

The economic burden of nosocomial infections can be assessed from different payer perspectives. Each perspective includes the costs that are relevant to decision makers from that perspective. Four major perspectives are used to conduct economic evaluations of healthcare interventions: 1. Hospital perspective 2. Third party payer perspective 3. Patient perspective 4. Societal perspective. Hospital administrators and executives may be interested in determining the burden of nosocomial infections from the hospital perspective. The direct costs of hospitalization such as infection attributable excess length of stay including intensive care unit stay, diagnostic testing, antimicrobial treatment, healthcare worker time, and isolation supplies (i.e., gloves, gowns, and masks for contact isolation or private rooms for respiratory isolation) are the only costs included from the hospital perspective.[11] Third party payers, such as insurance companies, also have a vested interest in the costs of nosocomial infections. Assessing the economic burden of nosocomial infections from the third party payer perspective includes both inpatient and outpatient expense. Direct medical costs (excluding isolation supplies) are accounted for as well as outpatient costs such as clinic visits, antimicrobial therapy,

rehabilitation visits as well as home health visits.[11] Performing economic evaluations from the third party payer perspective is important because payers can have a pivotal role in establishing which therapies are reimbursed.

The patient perspective is a third important perspective to consider when performing economic evaluations of healthcare interventions. Patients are often responsible for bearing at least a portion of the cost of their medical care and are also involved in making treatment decisions with their doctors. From the patient perspective all direct medical costs (both inpatient and outpatient) are accounted for as well as lost wages and travel expenses. Some have suggested that the cost of death may also be included when evaluating an intervention from the patient perspective.[11] Finally, economic evaluations can be performed from the societal perspective which is the most inclusive perspective accounting for the costs of disease to society. The societal perspective includes all direct inpatient and outpatient medical costs, lost wages, travel expenses, the cost of death, and in the case of nosocomial infections also accounts for the decreased effectiveness of antimicrobial agents overall, and further increases in antimicrobial resistance.[11] Each perspective appeals to a different set of decision makers who are evaluating the impact of nosocomial infection prevention measures.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a nosocomial pathogen of particular importance due to its substantial attributable morbidity and mortality. *S. aureus* is commonly found on the skin and in the nares of healthy individuals. Carriers of *S. aureus* are asymptomatic but are able to transmit *S. aureus* to others. Data from the 2001-2002 National Health and Nutrition Examination Survey (NHANES) found that the prevalence of colonization with any strain of *S. aureus* in the nares was 31.6% and that intranasal MRSA colonization prevalence was 0.84%.[12] NHANES data from 2002-2003 showed a statistically significant

decline (P<0.01) in the prevalence of *S. aureus* colonization to 28.6% compared to the 2001-2002 data, although there was an increase in MRSA prevalence to 1.5% (P<0.05).[13] This sample of the noninstitutionalized U.S. population >1 year old illustrates that *S. aureus* colonization is a prevalent commensal organism. Population estimates by Kuehnert and colleagues, also using the 2001-2002 NHANES data, for *S. aureus* colonization were 89.4 million individuals (95% confidence interval (CI): 84.8-94.1 million people).[14] MRSA colonization was estimated to be present in 2.3 million people in the United States (95% CI: 1.2-3.8 million MRSA colonizations).[14] Colonization prevalence was found to vary by age and was significantly higher in 6-11 year olds (p<0.001) than in the reference group of 1-5 year olds, and tended to decrease as age increased after age 11.[14] Multivariate analyses found that MRSA colonization was associated with being a woman older than 60 when the reference group was men 1-19 years old.[14] However it is unclear why this study utilized different age stratification schemes for univariate versus multivariate analyses. *S. aureus* heterogeneously impacts different genders, race/ethnicities, and ages of people. It is estimated that approximately 60% of the population is intermittent carriers of MRSA. These individuals are colonized for variable durations with strains of *S. aureus* that change over a period of time.[15] Persistent carriers account for approximately 20% of the population are colonized with the same strain of *S. aureus* that does not appear to change over time.[15] The remaining portion of the population appears to be noncarriers of *S. aureus* and these people are never known to be colonized with any strains of *S. aureus*.[15] The host factors that contribute to which category an individual may fall into have not been well studied and further research is needed.

The Active Bacterial Core surveillance (ABCs)/Emerging Infections Program Network uses active population-based surveillance to estimate the annual incidence of invasive MRSA

infections of nine sites in the U.S. that includes more than 16.5 million individuals (approximately 5.6% of the U.S. population).[16-17] This system utilizes regular contact with the hospital laboratories that confirm MRSA diagnoses to capture data regarding the incidence of invasive MRSA infections unlike passive surveillance systems that rely on physicians reporting cases of disease to public health officials. The catchment area from 2004-2008 includes the following sites: 1. State of Connecticut 2. Atlanta, Georgia metropolitan area 3. San Francisco Bay area, California 4. Denver, Colorado metropolitan area 5. Portland, Oregon metropolitan area 6. Monroe County, New York 7. Baltimore City, Maryland 8. Davidson County, Tennessee 9. Ramsey County, Minnesota. From July 2004 through December 2005 the standardized incidence rate of invasive infections was 31.8 per 100,000 (range 24.4 to 35.2 per 100,000, excluding the outlier site, Baltimore City).[16] The estimated number of invasive MRSA infections in the U.S. during this period was 94,360 (interval estimate 72,850-104,000) and an estimated 18,650 (interval estimate 10,050-22,100) MRSA deaths.[16] More recent data, from 2005 to 2008 noted a statistically significant 9.4% per year decrease in the number of invasive hospital-onset MRSA infections.[17] This decrease was observed in both hospital-onset and healthcare-associated community onset disease.[17] However, from 2005 through 2008 morbidity was substantial with more than 21,000 invasive infections occurring in the study population, making MRSA an important pathogen to study.[17]

Nosocomial infection prevention measures may allow a significant number of MRSA cases to be averted. Consensus has yet to be reached about the ultimate epidemiologic and economic value of various MRSA prevention strategies.[18] Because the majority of individuals with MRSA are asymptomatically colonized, these individuals are a potential reservoir for transmission within a healthcare setting.[19-25] Active surveillance for MRSA colonization of all

individuals in a healthcare setting (i.e., within a single ward such as the intensive care unit (ICU) or across all admissions to an acute care hospital) has been suggested as infection control strategy.[26-31] In this context, active surveillance is systemic testing of a defined population of individuals in a healthcare setting to identify those individuals who are asymptomatic carriers of MRSA. Debate remains over which surveillance method should be used: polymerase chain reaction (PCR) or culture based surveillance. PCR allows for rapid surveillance results in approximately one hour whereas culture based surveillance takes 18-48 hours.[32] Turnaround time can impact how quickly infection control personnel are able to implement isolation measures and/or decolonization. Sensitivity and specificity of different laboratory assays can vary dramatically; a recent study found that the sensitivity of various commercial culture-based assays can range from 81-93% for MRSA Select® to 96-100% for CHROMagar MRSA®.[32] Specificity of culture based methods was shown to range from 69-87% for Brilliance MRSA Agar® to 98-99% for BBL-CHROMagar®.[32] Cost is also a consideration when choosing a surveillance method. The Centers for Medicare & Medicaid Services (CMS) reimburses only $12.34 for culture based testing versus $50.26 for PCR, which can potentially influence the ultimate economic value of a surveillance strategy.[33] Moreover, there can be a difference between test cost and reimbursement. Choosing a MRSA testing strategy is a balance of test attributes, local epidemiological and economic conditions and laboratory capabilities.

Once carriers are identified, surveillance must be paired with an intervention such as decolonization, isolation, and/or cohorting of known carriers to decrease intra-hospital transmission.[34] Decolonization (the use of chemoprophylaxis to remove *S. aureus* from a colonized individual's body) is another infection control strategy that often accompanies active surveillance.[32] Debate remains over the efficacy of decolonization and if patients are to be

decolonized, which antimicrobial agents ought to be used.[35-37] Decolonization regimens often include intranasal mupirocin, chlorhexidine body washes and/or oral antibiotics.[37] However, resistance to decolonization agents, such as mupirocin has been commonly documented with widespread use of mupirocin in the general patient population and with routine use of mupirocin in peritoneal dialysis patients at the nasal and hemodialysis catheter exit sites.[38]

Isolation and cohorting of known MRSA carriers is a second strategy that is often used in conjunction with an active surveillance strategy. Rather than eliminating colonization, isolation strategies remove potentially infectious individuals from populations of susceptibles to minimize transmission within healthcare settings. Cohorting of colonized or infected individuals is used to prevent transmission when private rooms may not be available or in units such as the neonatal intensive care unit (NICU) where common rooms are the norm. Cohorting has been used in the NICU and long-term care facilities as a part of outbreak response.[39-43] Isolation of known MRSA carriers is recommended by the Joint Working Party of the British Society for Antimicrobial Chemotherapy and the Hospital Infection Society and the Society for Healthcare Epidemiology of America (SHEA).[44-45] SHEA also recommends decreasing unnecessary patient contact that may facilitate transmission of nosocomial pathogens, although a systematic review found that there is the potential for adverse psychological patient effects and decreased healthcare worker contact for patients in isolation.[45-46]

Increased education of healthcare workers about MRSA transmission and proper hand hygiene techniques are also important tenets in most MRSA prevention and control programs.[47] Without adherence to basic infection control strategies, such as adherence to hand hygiene protocols, surveillance and isolation of known carriers is unlikely to be a successful strategy in preventing nosocomial transmission. Many nosocomial infections, including MRSA, are spread

by direct contact of healthcare workers and patients. Unfortunately, measuring hand hygiene adherence can be difficult and the quality of the evidence that increased hand hygiene causes a direct decrease in infection rates is of poor quality.[48] Despite these limitations including increased hand hygiene as a part of a nosocomial infection prevention program remains an integral factor for a program's ultimate success.

Judicious use of antimicrobials as a part of an antimicrobial stewardship program is also a potential MRSA prevention strategy. Antimicrobial stewardship programs restrict the use of certain antibiotics by educating prescribers, limiting the antibiotics available on the facility's formulary, and requiring preapproval for the use of antibiotics included in the stewardship program.[49-50] Additionally, stewardship programs can incorporate antibiotic cycling, combination therapies, dose optimization, conversion from parenteral to oral therapy, and multidisciplinary teams to audit the use of antibiotics.[51] These programs endeavor to eliminate unnecessary and suboptimal usage of antibiotics, which some studies estimate accounts for 50% of antibiotic usage.[51-53] Debate remains over the implementation of stewardship programs because of difficulty of implementation and accurate measurement of the success of the programs. Quantifying the economic costs and benefits of such programs remains difficult despite a systematic review showing that stewardship programs can reduce antimicrobial resistance or nosocomial infection.[53] Well designed prospective studies will allow a better understanding of the economic and epidemiologic value of stewardship programs.

Modeling and simulation can provide insights into the economic and epidemiological value of nosocomial infection prevention and control strategies. Simulation models can aid in establishing the burden of nosocomial infections and can aid in the prioritization of different prevention and control measures.[54] Modeling allows investigators to conduct studies that would

not be feasible due to cost constraints or ethical to conduct in real patient populations. For example, stochastic simulation models can evaluate the economic value of numerous preoperative screening and decolonization strategies benchmarking appropriate decolonization regimens, screening strategies, and costs.[6, 55-56] Early in the development of vaccines for nosocomial infections, models can aid vaccine developers in determining appropriate target populations and efficacy thresholds.[57-59] Models can also evaluate infection control strategies, such as increased environmental cleaning, staff exclusion policies when healthcare workers are ill, isolation of symptomatic patients, and ward closure to new admissions when there is an outbreak.[60] Across the spectrum of infection prevention and control strategies modeling can be used as a complement to traditional studies.

Data used to calibrate models relies on published epidemiological studies. These data are derived from studies of variable study design, sample size, and duration. Computational modeling can bridge gaps in the exist in the current body of literature utilizing sensitivity analyses to determine the potential impact of disease characteristics that are known to vary geographically, temporally, or among different patient populations. Retrospective cohort studies are often performed to better understand if there is an association between exposures of interest and incidence of disease or a related outcome. However, when studying nosocomial infections such as MRSA that have a large proportion of individuals with disease who are asymptomatic carriers, retrospective studies that rely on medical records for participant classification would likely underestimate the asymptomatic burden of disease.

A retrospective cohort study by Allard and colleagues evaluated the changes in MRSA bacteremia incidence and mortality among patients at Centre Hospitalier Universitaire de Sherbrooke in Quebec, Canada, by reviewing medical records. MRSA bacteremia did not

emerge in the medical records of this hospital's population until 2000 although the study period commenced in 1991.[61] Due to the retrospective design of this study it is unclear if medical records in this hospital did not include the combination of ICD-9 codes for MRSA due to hospital policies for medical record coding, a lack of susceptibility testing that is necessary to diagnose MRSA, or due to actual temporal changes in MRSA incidence. This study compared patients with MRSA to those who had MSSA. Patients with MRSA bacteremia were significantly older than those patients with MSSA bacteremia (45% of patients were 18-64 with MSSA versus 30% of patients 18-64 with MRSA, P=0.02). MRSA patients also had significantly higher Charlson scores than those patients with MSSA (70% of patients with MRSA had a Charlson score $\geq$4 compared to 51% of patients with MSSA, P=0.01) and patients with MRSA were less likely to have effective treatment administered within the first 24 hours (77% versus 48% effectively treated for MSSA and MRSA, respectively, P<0.001). Incidence of bacteremia from 2000-2005 ranged from 2.6-7.4 per 100,000 residents of Sherbrooke, Quebec. Among sixty-nine patients with invasive bacteremia, twenty-three patients had died within 30 days of diagnosis (i.e., 33.3% mortality).

A retrospective cohort study that included review of medical records by Carey et al. from a level III NICU of a University-affiliated Children's Hospital in New York, New York from 2000-2008 provided data on both the prevalence and natural history of MRSA in neonates.[5] This hospital did not perform routine surveillance of neonates who were in-born, although they did perform routine surveillance of the anterior nares and preemptive isolation of neonates who were transferred from other facilities who accounted for 25%-30% of the NICU population. This sampling methodology would likely underestimate the total number of in-born asymptomatic carriers in the NICU. This hospital also experienced was a series of four outbreaks of MRSA

during 2007 that led to increased MRSA testing of not only the anterior nares, but also the periumbilical area, axilla, and groin. During this outbreak all neonates who shared the same pod as an infected neonate had surveillance cultures performed. When asymptomically colonized neonates were identified during this outbreak all other neonates in the same wing of the NICU were tested for MRSA colonization. Throughout the study period there were 98 neonatal MRSA infections that were utilized to calibrate the clinical MRSA infections outcomes subtree as well as the annual MRSA incidence. Computational models utilize the variable incidence data (ranging from 2 incident infections per 1,000 discharges in 2008 to 18 incident infections per 1,000 discharges in 2002) to determine the economic and epidemiologic impact of performing systematic NICU surveillance under a variety of local circumstances.

A third retrospective cohort study was also utilized to calibrate the computational models described in later chapters. This study that spanned seven years conducted at Brigham and Women's Hospital (Boston, MA), medical records of all neonates admitted to the NICU throughout the study period were reviewed. Whether inborn or transferred from other facilities, all neonates during this period were screened on a weekly basis for MRSA with a single swab of both the anterior nares and then the rectum.[62] Of 7,997 neonates admitted throughout the study period, 102 were identified as MRSA positive through screening, additionally, there were 15 neonates who had clinical MRSA infections. There were no significant differences in birth history, time to positive culture, clinical status at the time of the first positive culture, or maternal factors in those neonates who were colonized versus those with clinical infections. Sixty-three of 102 neonates in the study were discharged as asymptomatic MRSA carriers because the hospital protocol did not include decolonization. With a small sample size of neonates with clinical

MRSA infections, there may be questions of generalizability of the infection outcomes described in this study.

Prospective cohort studies that follow a defined group of individuals forward through time can also be used to calibrate computational models. However, these types of studies can be difficult to conduct in hospital settings because patients are admitted and discharged to hospitals with variable lengths of stay. Moreover, prospective cohort studies can be expensive to conduct. Relatively few prospective cohort studies are conducted to study infections within hospital settings. A prospective observational study by Ellis and colleagues performed nasal screening on U.S. military recruits and documented the natural history of MRSA.[20] On the first day of training of new recruits arriving at Fort Sam Houston, Texas, cultures of the anterior nares and demographic data were collected from all study participants. A second culture was collected from each recruit eight to ten weeks after the initial swab was collected to assess changes in colonization and infection status of the study participants over time. This population of military recruits was 76% male with a mean age of 21.1 years old, range 18-44 years old. Of 761 recruits who were sampled at both time points, 24 of 761 (3.15%) had a positive culture for MRSA at least one of the two samples. The prospective design of this study allowed for a point prevalence estimate of MRSA colonization in health young adults. Further, as a prospective cohort study, these investigators were able to describe changes in MRSA over a ten week period. The small number of individuals with MRSA and relatively short follow-up only allowed for observation of the most common clinical outcomes.

Cross sectional epidemiological studies are often conducted by investigators to determine point prevalence of disease. Cross sectional studies are much shorter in duration than prospective cohort studies and are therefore less expensive. By definition, cross sectional studies provide

data for a more limited period of time than cohort studies and may be less generalizable for diseases that vary temporally. Data regarding the sensitivity of MRSA surveillance by number of anatomic sites cultured are from a single cross-sectional study performed at two tertiary care facilities in Philadelphia, Pennsylvania: 1.The Hospital of the University of Pennsylvania (HUP) 2.The Children's Hospital of Philadelphia (CHOP).[63] Surveillance was performed simultaneously on five anatomic sites by both medical staff and patient (or patient's parents) immediately after: 1.Nares 2.Axillae 3.Throat 4.Groin 5.Perineum. The sensitivity of each culture was then determined comparing each individual, pair, or triplet of surveillance cultures to the gold standard of any positive culture from any anatomic site. The study population was comprised of 56 total participants: 49 adults and seven children. The investigators concluded that multiple surveillance sites were required to achieve sensitivity of ≥90%, although a single culture of the anterior nares in adults 84% sensitivity (95% CI: 71%- 92%).[63] These data were utilized to model the variable sensitivity and cost (i.e., number of anatomic swabs collected) of MRSA testing strategies. These data were collected from a single city over a relatively short period of time, and they may not be generalizable. Computational modeling allows investigators to determine the economic and epidemiologic impact of variable MRSA prevalence utilizing point prevalence estimates from multiple cross sectional studies as upper and lower bounds of sensitivity analyses.

Previous studies have evaluated the economic value of MRSA surveillance strategies and isolation protocols in adult inpatients, the incremental benefit of adding decolonization to an infection control program that already includes surveillance and isolation of positive patients, and the impact of PCR testing on MRSA bacteremia mortality rates.[64-66] Each of these investigators came to the conclusion that MRSA surveillance and accompanying isolation or

decolonization was a cost-effective strategy. However, in a model developed by Murthy and colleagues utilizing clinical data from a Swiss teaching hospital that evaluated the economic value of universal PCR concluded that surveillance was not a cost-effective strategy because of their local epidemiological circumstances.[67] This study assumed a very low baseline probability of MRSA infection of 0.0612 that may have contributed to the study's conclusions.[67] Moreover, clinical studies conducted in different healthcare facilities have utilized different MRSA tests as a part of their respective universal surveillance programs. Some investigators have used rapid PCR, others have utilized batched PCR protocols, and the remaining studies have implemented culture-based surveillance either with or without broth enrichment. Further analyses are needed to delineate the impact of local epidemiological circumstances and test characteristics on the ultimate economic value of MRSA surveillance strategies.

A joint statement issued by the Society for Healthcare Epidemiology of America (SHEA), the Association for Professionals in Infection Control and Epidemiology (ACIP), the Pediatric Infectious Disease Society (PIDS), the Infectious Disease Society of America (IDSA), the Council of State and Territorial Epidemiologists (CSTE), the Association of State and Territorial Health Officials (ASTHO), and the CDC called for the elimination of healthcare associated infections.[68-69] These groups defined the elimination of nosocomial infections as, "the maximal reduction of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required."[68-69] A four pillared strategy was proposed including: 1. Evidence-based prevention efforts 2. Alignment of incentives 3. Innovative research 4. Data for action and responding to emerging diseases. The statement created a broad framework of infection prevention strategies and highlighted the importance of eliminating the nosocomial infections.

Each of the nosocomial infection prevention strategies described in the following chapters could be used by hospital administrators to move towards the CDC goal of eliminating nosocomial infections. The following chapters model the epidemiological and economic impact of changing surveillance test attributes, target populations, and intervention implementation strategies.

2.0 ALL METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) TESTS ARE NOT CREATED EQUAL: A COMPARATIVE ECONOMIC SIMULATION MODEL

2.1 ABSTRACT

Controversy remains over the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence, net reproductive rate (R), anatomic sites tested (individually plated and plated together), turnaround time, and efficacy of contact isolation in preventing secondary cases on the ultimate economic value of MRSA testing. We developed a stochastic computer simulation model from the third party payor perspective to evaluate the differential impact of these parameters on the economic value of testing. MRSA prevalence, R, turnaround time, and contact isolation efficacy were major drivers of the cost effectiveness of surveillance. When R is 1.0 and prevalence is 1% given a one day turnaround time the cost per case averted was $74,439 with an incremental cost-effectiveness ratio (ICER) (i.e., dollars spent per quality-adjusted life year saved) of $11,110. With two day turnaround, the cost per case averted increased to $156,802 and ICER increased to $29,207. Similarly, as isolation efficacy increased from 25% to 50% to 75%, cost per case averted decreased: 43,725 to 20,406 to 11,110 for one day turnaround. Decision makers should choose MRSA testing strategies with shorter turnaround time and work

to increase the efficacy of contact isolation protocols. Testing multiple anatomic sites whether on multiple plates or a single plate does not substantially improve the economic value.

2.2 BACKGROUND

Testing patients for methicillin-resistant *Staphylococcus aureus* (MRSA) may be a key intervention to control the spread of the pathogen, a substantial and continuing problem in healthcare facilities.[16, 70] However, controversy remains over the number of anatomical sites that ought to be tested and the potential impact of turnaround time on the overall value of MRSA testing.[30, 71-72] Testing protocols differ among healthcare facilities, and may affect the ultimate economic value of surveillance programs and other MRSA testing strategies.[72-75] Therefore, not all MRSA testing strategies are equivalent. Understanding how such laboratory logistical questions may significantly impact the economic value of MRSA testing is important for making informed decisions.

Ultimately, the optimal MRSA test and testing strategy is a balance of costs and potential benefits. Culturing more anatomic sites increases testing sensitivity, potentially identifying more asymptomatic carriers, but at the same time increases costs (e.g., increases the number of swabs and personnel time to collect and test the samples). Decreasing turnaround time reduces the time that carriers may transmit to others before being isolated, but also may bring additional costs (e.g., more costly rapid tests and information systems to transmit results back to the hospital floor). We developed a stochastic computer simulation model to evaluate the economic impact of varying different testing characteristics such as test turnaround time, sensitivity, specificity, cost per test, and the number anatomical sites swabbed. Sensitivity analyses also explored the impact

of ranging MRSA prevalence, effectiveness of isolation in preventing secondary transmission, and net reproductive rate (R).

2.3 METHODS

2.3.1 Model Structure

Figure 2.1 outlines the general structure of the stochastic simulation model developed using TreeAge Pro 2009 (TreeAge Software, Williamstown, MA) and Microsoft Excel (Microsoft Inc, Redmond, WA). Upon admission to an acute care hospital, each patient (median age: 40 years) has a probability of being MRSA colonized (MRSA prevalence) either undergoes or does not undergo MRSA screening of a single anatomical site (nares, throat, groin, perineum, or axillae), two anatomical sites (nares and throat, nares and groin, nares and perineum, nares and axillae), or three anatomical sites (nares, throat and groin; nares, throat and perineum; nares, throat and axillae). The number of sites tested affects the overall test cost, sensitivity, and specificity.

Experiments varied the turnaround time to receive results and implement isolation for those with positive results between 1 and 2 days. A positive test (either true or false positive) resulted in a patient being placed on contact isolation, regardless of the patient's true colonization status. Contact isolation reduced the probability of the patient transmitting MRSA to non-colonized patients. R determined the number of additional cases generated by each MRSA colonized patient that was not placed on contact precautions. Each of these additional cases could remain asymptomatically colonized or develop clinical infection resulting in any

combination of the following clinical sequelae (shown in Figure 2.2): abscess, bacteremia, cardiac surgery (prerequisite: endocarditis), cellulitis, endocarditis, line infection, pneumonia, osteomyelitis, septic shock (prerequisite: bacteremia), urinary tract infection (UTI), and wound infection (e.g., one MRSA colonized patient could develop only cellulitis while another could develop a line infection and bacteremia). The clinical sequelae determined the MRSA-attributable mortality. Each clinical sequela required vancomycin for treatment of the following durations: endocarditis, 4-6 weeks; osteomyelitis, 6 weeks; UTI, 3-5 days; all others, 10-14 days. Clinical probabilities came from an extensive MEDLINE literature search which excluded case reports and case series and studies published prior to 2000, since prior standard of care may have differed from current practices.

Table 2.1 outlines the diagnostic and therapeutic procedures, hospitalization costs, and quality adjusted life-year (QALY) decrements associated with each clinical sequela and its respective distribution. Patients with multiple sequalae were only assessed the cost of hospitalization for their most severe condition. A 3% discount rate converted costs to 2009 US dollars. The model assumed the third party payor perspective, and each simulation run consisted of 1,000 trials of 1,000 individuals or a total of 1,000,000 simulated patients traveling through the model. A one year time horizon was employed by the model. Comparable model methods are described in detail by Lee et al.[64]

The primary model outcome measure was the incremental cost-effectiveness ratio (ICER), where cost is measured in dollars and effectiveness in quality-adjusted life-years (QALYs).

ICER = (Cost with MRSA Testing - Cost without MRSA Testing) / (Effectiveness with MRSA Testing - Effectiveness without MRSA Testing).

Interventions with ICER values below $50,000/QALY are generally accepted to be cost-effective.[76] A secondary model outcome measure was the cost per case of MRSA averted, where a case is defined as either a symptomatic or asymptomatic secondary MRSA infection.

Cost Per Case Averted = (Cost with MRSA Testing - Cost without MRSA Testing) / (Secondary Cases Without MRSA Testing – Secondary Cases with MRSA Testing).

2.3.2 Sensitivity Analyses

Sensitivity analyses systematically varied key model parameters such as MRSA prevalence (i.e. probability of colonization) from 0.1% to 25%[12-13, 16-17, 20-22, 35], R from 0.25 to 2.0[77], turnaround time from 1 to 2 days[28, 74, 78], contact isolation efficacy from 25% to 75%[48, 79-80] (to represent variations in adherence to hand hygiene and contact isolation protocols), number of anatomic sites screened[63], and the impact of screening multiple anatomic sites with a single agar plate (and single charge for surveillance).

2.4 RESULTS

The cost-effectiveness of surveillance was most impacted by local MRSA conditions (MRSA prevalence and R), turnaround time, and efficacy of isolation. Outcomes were less sensitive to anatomic sites tested, even when multiple cultures were analyzed on a single culture plate. As turnaround time increased, ICER value also increased, indicating that surveillance

results in a shorter time were more cost-effective. Additionally, as MRSA prevalence increased, testing became increasingly cost-effective.

2.4.1 *Local Prevalence and R*

As local MRSA conditions became more severe (i.e. higher local MRSA prevalence and/or R) surveillance became increasingly cost-effective. Table 2.2 shows the ICER values decreased as both prevalence and R increased. This is true across all turnaround time, isolation efficacy, and sites cultured scenarios tested. Cost per case averted follows this same pattern, with decreasing cost per case averted as prevalence and/or R increased.

2.4.2 *Effects of Turnaround Time*

Turnaround time for culture results and the implementation of contact precautions had a considerable impact on the economic value of a surveillance program. As turnaround time increased, the economic value of surveillance decreased. When a single culture of the anterior nares was utilized, isolation had a 75% effectiveness, R=1.0, and prevalence was 1%, the ICER value was $11,110/QALY with a one day turnaround and increased to $29,207/QALY with a two day turnaround time. Similarly, for these same scenarios the cost per case averted was $74,439/case for a one day turnaround and more than doubled to $156,802/case for a two day turnaround.

2.4.3 *Efficacy of Isolation*

The efficacy of isolation in preventing secondary cases of nosocomial MRSA had a considerable impact on both the ICER values and cost per case averted. With increasing isolation efficacy the economic value of surveillance increased. When R was 0.5, the prevalence of MRSA was 5% as isolation efficacy increased from 25% to 50% to 75% the ICER values for a single culture of the anterior nares with a two day turnaround time decreased as follows: $45,155/QALY to $17,703/QALY to $10,875/QALY. For these same scenarios the cost per case of MRSA averted decreased from $198,851/case to $103,498/case to $68,038 with increasing efficacy of isolation.

2.4.4 *Number of MRSA Colonizations and Infections Prevented*

The efficacy of isolation also impacted the number of secondary MRSA cases and infections. For scenarios where R was 0.5 and the prevalence of MRSA was 5%, without surveillance and isolation of those who tested positive there were a mean of 18.53 colonizations and 6.55 clinical infections. With low efficacy of isolation (i.e., 25%) 17.33 colonizations and 6.07 clinical infections remained a decrease of only 6.52% and 7.35% for colonizations and clinical infections, respectively, from the baseline scenario without surveillance and isolation. As efficacy of contact isolation increased to 50%, there was a 14.31% and 14.11% decrease in MRSA colonizations and clinical infections, respectively, with 15.88 colonizations and 5.63 clinical infections remaining. When efficacy of isolation was 75%, the greatest decline in MRSA cases was seen with a decrease of 20.08% of colonizations and 20.58% of infections.

2.4.5 *Impact of Screening Multiple Anatomic Sites*

When each anatomic site is cultured on a separate agar plate there is not a clear correlation between number of anatomic sites cultured and the economic value of surveillance. When isolation efficacy was 75%, turnaround time was 2 days, MRSA prevalence was 5%, and R was 0.5, the ICER actually increased slightly with an increasing number of sites: testing the nares only, a pair of cultures of the nares and throat, and a triplet of cultures of the nares, throat, and axillae. For these scenarios ICER values increased from $10,875/QALY to $11,432/QALY to $11,649/QALY and the cost per case averted also increased from $68,038/case to $76,601/case to $82,249/case, respectively. Economic value of surveillance decreased (i.e., had a higher ICER value) as number of anatomic sites cultured on unique plates increased.

2.4.6 *Plating Multiple Cultures on a Single Plate*

When multiple surveillance swabs are plated together and the patient is only charged for a single test ($50), surveillance of multiple anatomic sites became increasingly cost-effective. When isolation efficacy was 75%, turnaround time was 2 days, MRSA prevalence was 2.5%, and R was 1.0, the ICER decreased from $12,042/QALY for a culture only of the anterior nares to $10,383/QALY for a pair of cultures of the nares and throat to $8,907/QALY for a triplet culture of the nares, throat and axillae when cultured on a single agarose plate. The cost per case averted for these scenarios displayed a similar pattern, decreasing from $190,475/case to $183,701/case to $174,780/case for the nares only, nares and throat cultures, and nares, throat, and axillae scenarios, respectively. These scenarios display some stochasticity, given MRSA prevalence of 25% and R of 0.5, the same three testing strategies' ICERs are $3,556/QALY, $3,826/QALY,

and $3,595/QALY, respectively. Each of these testing strategies is strongly cost-effective falling well below the $50,000/QALY threshold. Cost per case averted for these scenarios ranges from $62,173/case to $66,749/case.

2.5 DISCUSSION

Our analyses demonstrate the paramount importance of test turnaround time and contact isolation effectiveness in determining the economic value of MRSA testing. In other words, all MRSA testing and surveillance strategies are not the same, which may explain the varying economic value of surveillance found by previous clinical studies and economic models.[55, 64, 70, 72-75, 81-82] This suggests that both future clinical studies and infection control guidelines ought to clearly outline the MRSA test characteristics, protocols following positive test results, and adherence to contact isolation protocols.

Olchanski and colleagues developed an Excel-based Monte Carlo simulation model that assessed the impact of test characteristics on the clinical and economic value of MRSA testing in U.S. hospitals.[83] This model evaluated the impact of a variety of MRSA testing strategies both culture based and PCR. However, this study had a mean MRSA-attributable LOS of 9 days (range: 4-12 days) which is substantially longer than the MRSA-attributable LOS utilized in our analyses and a lower test cost utilized in sensitivity analyses of $5-$25. Both of these parameter estimates may impact the ultimate economic value of a MRSA testing strategies. Further, our analyses also evaluated the economic value of surveillance by anatomic site cultured which provides further insight to decision makers choosing a surveillance strategy to implement in their facility.

Our study may help guide future development of MRSA tests. Aiming for rapid turnaround times may be more important than increased sensitivity afforded by either testing more anatomic sites or an inherent characteristic of the test itself. Budgetary constraints often dictate how MRSA testing protocols are implemented. When considering a MRSA surveillance program, decision makers must decide which aspects of testing to prioritize. Increased sensitivity requires additional cultures, which our results suggest are not justified by the additional testing cost. Developers of MRSA tests should aim to minimize turnaround time, whether by polymerase chain reaction (PCR), enhanced broth enrichment, or by way of a novel approach. Computational models can help decision makers understand what the potential economic impact of enhancing different test characteristics may be. To increase the sensitivity of MRSA testing strategies, broth enrichment is often utilized. The longer that is sample is enriched, the higher the sensitivity, although this is a non-linear increase. Therefore, understanding the benefit that a less sensitive rapid test may have in terms of both epidemiologic and economic outcomes compared to a more sensitive test that requires 48 hours or more of enrichment is valuable information for test developers.

Hospital decision makers can also utilize the results of our study. Infection control personnel can critically evaluate their testing and contact isolation protocols and use our model to benchmark the approximate economic value of MRSA testing in their respective facilities. Hospital administrators are able to evaluate their facility's adherence to isolation protocols as a metric of the potential value of a MRSA surveillance program in their facility. The widespread implementation of rapid testing methods or the use of information systems that quickly communicate results to nurses who place patients in isolation may be necessary for a MRSA surveillance program to be cost-effective and minimize the cost per case averted. Poor adherence

to isolation protocols results in less economically favorable MRSA surveillance programs. To mitigate the impact of low adherence to isolation protocols healthcare facilities may need to implement increased staff education, additional signage reminding medical and non-medical staff and hospital visitors that a patient is on contact isolation, or other local solutions that will increase adherence to isolation protocols.

2.5.1 *Limitations*

Models are a decision making aid, and are not meant as a replacement of classic epidemiological studies. When considering the optimal MRSA testing strategy, hospital administrators ought to consider local epidemiology of MRSA, available laboratory resources, infection control practices, and costs. We aimed to be conservative in estimating the economic value of MRSA testing, including only the most common sequelae and costs. Other studies[83] have utilized longer estimates of MRSA-attributable LOS and the accompanying costs of MRSA infections that may lead to differences in estimates of the economic value of MRSA testing strategies.

2.5.2 *Conclusions*

Choosing a MRSA testing method is a complex balance of test attributes. Our results suggest that the higher costs of multiple surveillance sites are not justified by the incremental gains in test sensitivity, and in fact, the test turnaround times may be a larger driver of the economic value of a MRSA testing strategy. Infection control guidelines that mandate MRSA surveillance need to be cognizant that not all MRSA testing programs are equally valuable.

Delaying the implementation of isolation protocols allows sufficient time for asymptomatic patients to transmit MRSA, substantially decreasing the economic value of testing. More widespread use of rapid MRSA testing methods that decrease the time that those individuals who are asymptomatically colonized remain in contact with those who are susceptible to MRSA acquisition, would likely increase the economic value of testing programs. Resources should be devoted to decreasing turnaround time to increase the economic value of MRSA testing and nosocomial infection rates.

2.6 FIGURES AND TABLES

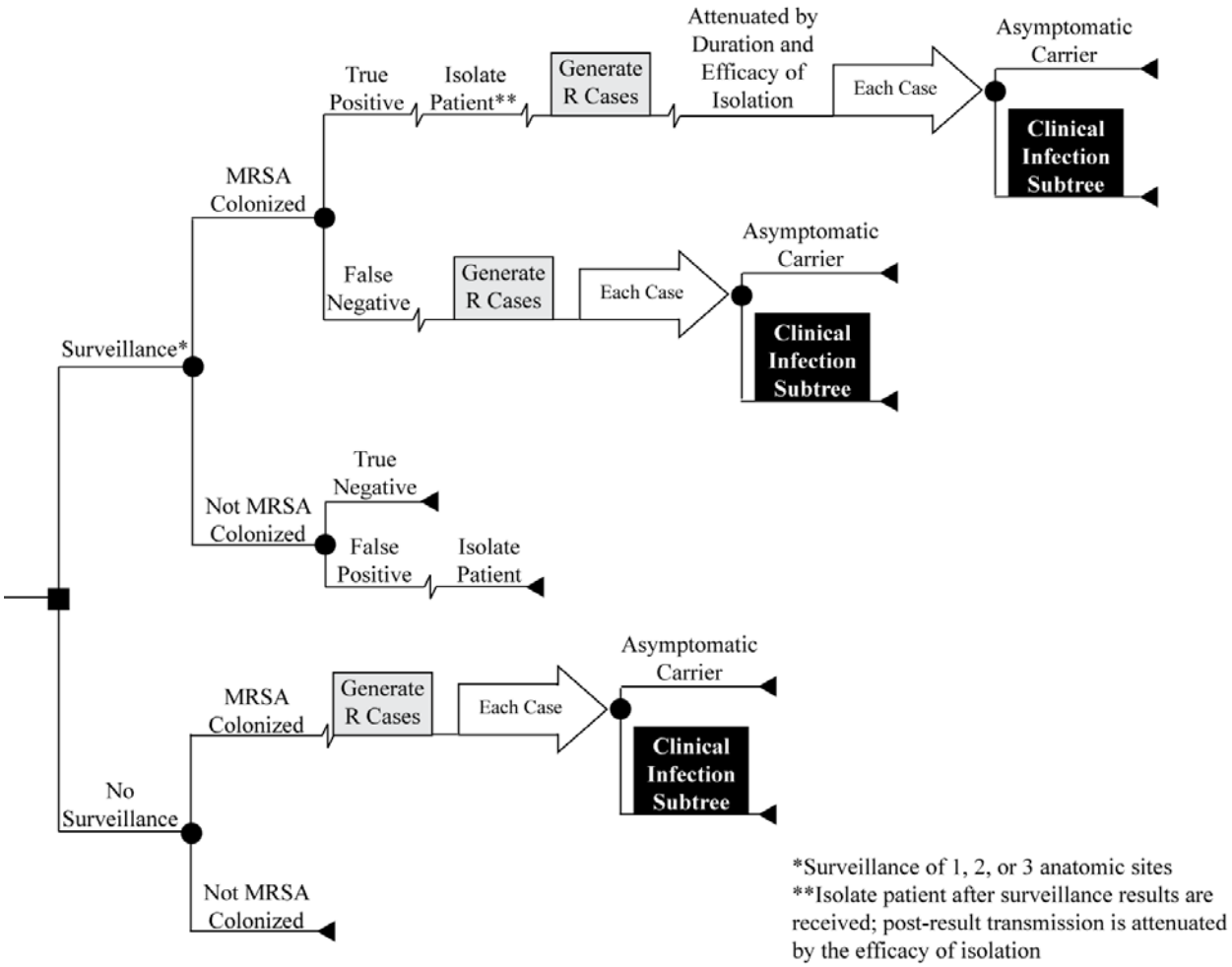

Figure 2.1: Model Structure

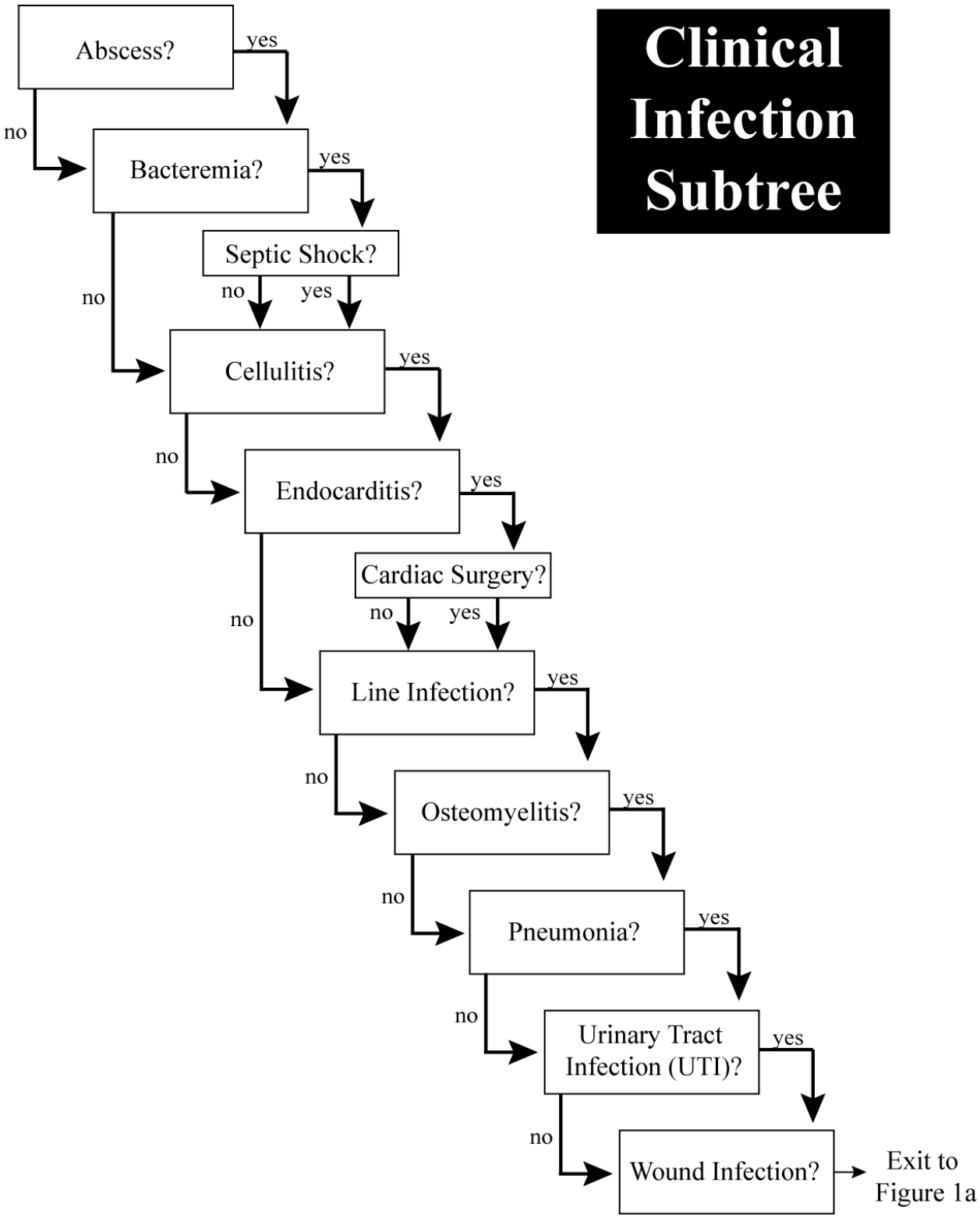

Figure 2.2: Clinical Infection Outcomes Subtree

[a] QALY decrements persist for 2 weeks.

Table 2.1: Model Inputs				
Model Parameter	**Mean Value**	**Range or Standard Deviation**	**Distribution Type**	**Source**
Costs (2010 US$)				
Contact Isolation	6,500	4,290-8,710	Triangular	[84]
Excess Hospitalization				
Abscess	3,877	534	Gamma	[85]
Bacteremia	8,250	416	Gamma	[85]
Cardiac Surgery	38,317	1,088	Gamma	[85]
Cellulitis	4,140	130	Gamma	[85]
Endocarditis	13,996	2,964	Gamma	[85]
Line Infection	11,717	3,277	Gamma	[85]
Osteomyelitis	8,694	963	Gamma	[85]
Pneumonia	13,498	463	Gamma	[85]
Septic Shock	13,772	4,344	Gamma	[85]
Urinary Tract Infection (UTI)	4,906	112	Gamma	[85]
Wound Infection	4,099	266	Gamma	[85]
Therapeutic and Diagnostic Procedures				
Blood cultures, 2 sets	31	21-42	Triangular	[86]
Cardiac surgery	1,278	843-1,712	Triangular	[85]
Computerized tomography, chest	244	161-327	Triangular	[85]
Echocardiogram, transesophageal	169	11-226	Triangular	[85]
Echocardiogram, transthoracic	170	112-227	Triangular	[85]
Incision and drainage	334	220-447	Triangular	[85]
Magnetic resonance imaging, extremity	479	316-641	Triangular	[85]
Orthopedic hardware replacement	1,779	1,174-2,384	Triangular	[85]
Peripheral intravenous line insertion	151	99-202	Triangular	[85]
Peripherally inserted central catheter insertion	290	191-389	Triangular	[87]
Radiograph, extremity	30	20-40	Triangular	[85]
Surgical replacement of graft	1,299	857-1,741	Triangular	[85]
Ultrasound, Doppler	128	84-171	Triangular	[85]
Urinalysis	6	4-9	Triangular	[85]
Urine culture	58	44-73	Triangular	[85]
Wound culture	50	42-58	Triangular	[88]
Wound debridement	72	47-96	Triangular	[85]
Test Characteristics	***Probability, %***			
Surveillance Sensitivity: Single Sites				
Nares Only	84	71-92	Triangular	[63]
Throat Only	65	51-78	Triangular	[63]
Axillae Only	31	19-45	Triangular	[63]
Groin Only	38	25-52	Triangular	[63]
Perineum Only	40	27-54	Triangular	[63]

Table 2.1: Continued

Test Characteristics	*Probability, %*			
Surveillance Sensitivity: Combinations of Sites				
Nares and throat	91	80-97	Triangular	63
Nares and axillae	85	73-94	Triangular	63
Nares and groin	85	73-94	Triangular	63
Nares and perineum	87	76-95	Triangular	63
Nares, throat, and axillae	93	82-98	Triangular	63
Nares, throat, and groin	98	90-100	Triangular	63
Nares, throat, and perineum	95	85-99	Triangular	63
Surveillance Specificity	97.1	92.2-99.5	Triangular	78
Invasive Infection, Given Colonization	26.00	17.65	Beta	19-25, 89
Sequalae, Conditional on Invasive Infection				
Abscess	4.17	3.13-5.21	Triangular	20
Bacteremia	27.70	31.42	Beta	90-95
Cardiac Surgery	38.87	32.46	Beta	92, 96-99
Cellulitis	37.04	32.62	Beta	94, 99-100
Endocarditis	33.33	20.66	Beta	91, 101-102
Line Infection	32.56	15.99	Beta	61, 96-97, 103-107
Osteomyelitis	13.54	10.16-16.93	Triangular	104, 108
Pneumonia	38.15	30.83	Beta	61, 90, 102-105, 107-109
Septic Shock	22.70	10.05	Beta	96-97, 107, 110
Urinary Tract Infection (UTI)	9.39	4.64	Beta	61, 94, 104, 107-108
Wound Infection	27.45	14.76	Beta	61, 90, 103-105
Mortality, by Sequela				
Bacteremia	29.38	--	--	61, 90, 93-95, 98, 103-109, 111-115
Cardiac Surgery	17.91	--	--	116-118
Endocarditis	40.71	--	--	61, 92, 96-97, 99, 101-105
Pneumonia	31.38	--	--	90, 93-95, 102, 119-122
Septic Shock	60.77	--	--	123
Utilities	*(Quality-Adjusted Life-Years (QALYs))*[a]			
Abscess	0.642	--	--	124-125
Bacteremia	0.530	--	--	124, 126
Cardiac Surgery	0.500	--	--	124, 127
Cellulitis	0.642	--	--	124-125
Endocarditis	0.530	--	--	124, 126
Line Infection	0.642	--	--	124-125
Osteomyelitis	0.530	--	--	124, 126
Pneumonia	0.580	--	--	124, 128
Septic Shock	0.530	--	--	124, 126
Urinary Tract Infection (UTI)	0.730	--	--	124, 128
Wound Infection	0.642	--	--	125

Table 2.2: Incremental Cost-Effectiveness Ratio (ICERs) (Cost per quality-adjusted life-year saved) by varying surveillance site, turnaround time, MRSA prevalence and net reproductive rate (R)

2 Day Turnaround Time				
	Net Reproductive Rate (R)			
Anatomical Site	**0.25**	**0.5**	**1.0**	**1.5**
MRSA Prevalence 1%				
Single Swab: Nares	46,936	52,772	29,207	18,052
Single Swab: Throat	163,343	120,991	34,853	24,235
Two Swabs: Nares & Throat	51,832	31,984	41,342	25,921
Three Swabs: Nares, Throat, & Axillae	339,547	44,964	34,065	19,561
MRSA Prevalence 2.5%				
Single Swab: Nares	47,027	24,336	9,674	8,501
Single Swab: Throat	36,563	23,244	14,355	9,782
Two Swabs: Nares & Throat	33,734	24,293	10,826	8,522
Three Swabs: Nares, Throat, & Axillae	34,431	24,372	15,124	9,035
MRSA Prevalence 5%				
Single Swab: Nares	29,129	10,875	5,919	3,815
Single Swab: Throat	26,542	18,496	6,413	5,275
Two Swabs: Nares & Throat	23,022	11,432	5,889	3,766
Three Swabs: Nares, Throat, & Axillae	16,465	11,649	7,070	5,132
MRSA Prevalence 15%				
Single Swab: Nares	7,756	4,897	2,658	1,478
Single Swab: Throat	10,378	5,529	3,024	1,699
Two Swabs: Nares & Throats	9,279	5,889	2,541	1,622
Three Swabs: Nares, Throat, & Axillae	12,281	5,831	2,791	1,844
MRSA Prevalence 25%				
Single Swab: Nares	6,906	4,212	1,742	1,072
Single Swab: Throat	7,874	4,620	1,887	1,587
Two Swabs: Nares & Throat	7,512	4,037	1,885	1,177
Three Swabs: Nares, Throat, & Axillae	8,613	4,631	1,918	1,258

Table 2.2: Continued				
1 Day Turnaround Time				
	Net Reproductive Rate (R)			
Anatomical Site	**0.25**	**0.5**	**1.0**	**1.5**
MRSA Prevalence 1%				
Single Swab: Nares	50,665	26,976	11,110	9,071
Single Swab: Throat	189,865	110,343	23,915	19,646
Two Swabs: Nares & Throat	2,145,655	62,090	34,509	25,007
Three Swabs: Nares, Throat, & Axillae	71,252	53,316	29,678	16,025
MRSA Prevalence 2.5%				
Single Swab: Nares	19,165	13,326	6,175	3,586
Single Swab: Throat	48,261	19,142	11,383	9,152
Two Swabs: Nares & Throat	43,793	44,788	11,434	8,069
Three Swabs: Nares, Throat, & Axillae	42,818	22,213	13,365	8,555
MRSA Prevalence 5%				
Single Swab: Nares	12,959	6,138	2,707	1,821
Single Swab: Throat	23,163	11,816	5,612	4,057
Two Swabs: Nares & Throat	23,761	13,554	6,023	4,400
Three Swabs: Nares, Throat, & Axillae	39,172	14,616	6,665	4,227
MRSA Prevalence 15%				
Single Swab: Nares	5,352	2,502	1,152	632
Single Swab: Throat	11,559	5,522	2,729	1,589
Two Swabs: Nares & Throats	10,846	5,173	2,347	1,661
Three Swabs: Nares, Throat, & Axillae	11,029	6,211	2,782	1,791
MRSA Prevalence 25%				
Single Swab: Nares	4,194	1,737	742	423
Single Swab: Throat	6,743	4,009	1,695	1,223
Two Swabs: Nares & Throat	8,023	3,524	1,903	1,153
Three Swabs: Nares, Throat, & Axillae	9,117	4,449	1,951	1,258

3.0 SHOULD NEWBORNS IN THE NEONATAL INTENSIVE CARE UNIT BE SCREENED FOR METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)?

3.1 ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a cause of substantial morbidity and mortality in the neonatal intensive care unit (NICU). Active surveillance in the NICU (i.e., testing all neonates to determine MRSA colonization status and increasing infection control precautions to prevent spread of the pathogen) has been suggested as an outbreak prevention measure and has been previously used in outbreak control. We developed a Markov simulation model that depicted the decision of whether or not to implement weekly agar-based surveillance in the NICU in a United States hospital from the third party payer perspective. Weekly surveillance for MRSA in the NICU was cost-effective across all scenarios we tested, with incremental cost-effectiveness ratio values <$10,000/QALY. As the annual MRSA incidence increased, the number of neonates needed to screen to prevent a single case of MRSA (i.e., colonization or infection) decreased. When R=0.5, annual MRSA incidence was 2.5%, and there was 50% isolation efficacy in preventing secondary cases of MRSA, 102 neonates would need to have weekly surveillance cultures to prevent a single MRSA case. Increasing contact isolation efficacy to 75% for the same scenario would decrease the NNS to 66 neonates. Our study

suggests that hospitals with moderate to high adherence to increased contact precautions protocols could benefit from the implementation of active surveillance. Hospitals ought to consider adding active surveillance for MRSA to a suite of NICU infection control precautions as an effective measure for preventing excess morbidity and mortality.

3.2 INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a cause of substantial morbidity and mortality in the neonatal intensive care unit (NICU), not only in the United States, but also worldwide.[5, 41-42, 129-136] Neonates in the NICU may have limited ability to mount a full immune responses, making them particularly vulnerable to MRSA infections.[137] Active surveillance in the NICU (i.e., testing all neonates to determine MRSA colonization status and increasing infection control precautions to prevent spread of the pathogen) has been suggested as an outbreak prevention measure and has been previously used in outbreak control.[41-42, 131, 134, 136] However, systematic MRSA testing of all neonates in the NICU can be a costly undertaking, and hospitals may have limited financial resources. Therefore, understanding the economic implications of infection control protocols before implementation is valuable for hospital decision makers. We constructed an economic simulation model to evaluate the potential economic value of active MRSA surveillance in the NICU.

3.3 METHODS

We developed a Markov simulation model that depicted the decision of whether or not to implement weekly agar-based surveillance in the NICU in a United States hospital from the third party payer perspective using TreeAge Pro 2009 (Williamstown, MA) and Microsoft Excel (Redmond, WA). Each newborn that entered the NICU had a probability of contracting MRSA based on the local hospital prevalence. All newborns received a single anterior nares culture upon admission to the NICU. Additionally, each received an additional weekly culture for the duration of stay. Length of stay (LOS) was pulled from a distribution of MRSA positive neonates or a distribution of Methicillin-susceptible *Staphylococcus aureus* (MSSA) neonates from a longitudinal NICU surveillance study.[5] Sensitivity analyses also varied this increased LOS with MRSA infection.

Each culture returned a positive or negative result based on the sensitivity and specificity of the surveillance test and a newborn's true colonization status. All newborns with a positive surveillance culture, whether a true positive or false positive, were placed under increased contact precautions for the remainder of that week. The cost of increased contact precautions was a function of the number of nurse contacts per day, the costs of gloves and gowns, and the nurse time required to don this personal protective equipment. Newborns with a negative culture, whether a true negative or false negative, were not placed under increased contact precautions; those newborns with a false negative surveillance result were able to transmit MRSA to other newborns in the NICU. Neonates who were colonized and did not have a surveillance culture were not placed under increased contact precautions and transmitted the net reproductive rate (R) cases to other neonates. Increased contact precautions attenuated, but did not eliminate, these secondary cases proportional to the efficacy of the contact precautions.

Figure 3.1a outlines the structure of the model. There were 3 mutually exclusive Markov states:

1. No MRSA colonization or infection

2. MRSA colonized or infected

3. No longer in the NICU (due to neonatal death or discharge from the NICU).

Each neonate occupied a state for the duration of a cycle (1 week) and then had a probability of transitioning to the other Markov states. All probabilities are outlined on Table 3.1. MRSA colonized neonates had a probability of developing a clinical infection.

All neonates with clinical MRSA infections were assumed to be placed under increased contact precautions, regardless of surveillance culture status. Figure 3.1b outlines the general flow of neonates in the model and Figure 3.1c outlines the clinical MRSA infection outcomes. In our study, clinical MRSA infections were defined as bacteremia, conjunctivitis, or skin and soft tissue infections (SSTIs). Each infection required the therapeutic and diagnostic procedures outlined on Table 3.1. Additionally, each infected neonate was treated with intravenous vancomycin. Dosing of vancomycin was based on a neonate's weight; a 10 day course of treatment was required for SSTIs and a 14 day course of treatment was the treatment for bacteremia. Conjunctivitis was treated with combination trimethoprim/polymyxin eye drops for 10 days. To convert past and future costs to 2010 dollars, we utilized a 3% discount rate.

Neonates who were colonized with MRSA and not placed under increased contact precautions (i.e. the neonates under the no surveillance branch of the model or those neonates with false negative surveillance cultures) were able to transmit MRSA to other neonates in the

NICU equal to R. Since R for MRSA is not well described in the literature, we systematically varied this parameter. When R=0.5, for every two MRSA cases in the NICU there was one secondary case in the NICU. Similarly, when R=1.5, for each primary case in the NICU, 1.5 secondary cases were produced. Neonates who were placed under increased contact precautions had an R value that was attenuated by the efficacy of isolation. However, these neonates were assumed to still transmit a fraction of the R value due to imperfect adherence to isolation protocols.

3.3.1 *Sensitivity Analyses*

Sensitivity analyses systemically varied key model inputs that are known to vary geographically and temporally. We performed sensitivity analyses for the following model inputs and respective ranges: annual MRSA incidence (1% to 15%)[39, 62, 129, 138-139], R (0.5-1.5)[77], efficacy of increased contact precautions in preventing secondary MRSA transmission in the NICU (25-75)[48], and relative increase in LOS for MRSA infection (10% to 33%)[42, 138-139]. Additionally, probabilistic sensitivity analyses simultaneously varied all parameters over their respective ranges on Table 3.1.

3.3.2 *Outcomes Measures*

The cost and number of neonates needed to screen to prevent one case (i.e., MRSA colonization or clinical infection) was the primary outcome assessed in the model. A secondary outcome was the incremental cost-effectiveness ratio (ICER). The ICER calculated the cost per

quality-adjusted life year (QALY) gained with surveillance. The following formula calculated the ICER for each simulation:

$$\text{ICER} = \frac{\text{(Cost with MRSA Surveillance – Cost without MRSA Surveillance)}}{\text{(Effectiveness with MRSA Surveillance – Effectiveness without MRSA Surveillance)}}$$

ICER values ≤ $50,000/QALY are generally regarded as cost -effective.[76] When surveillance was both less costly and provided better health outcomes (i.e., a higher effectiveness value) than no surveillance, it was regarded as the dominant strategy.

3.4 RESULTS

3.4.1 *General Results*

Weekly surveillance for MRSA in the NICU was cost-effective across a wide range of testing strategies and local MRSA conditions. With increasing efficacy of isolation in preventing secondary MRSA cases in the NICU, an increasing economic value of MRSA surveillance in the NICU was observed. Across all scenarios we tested weekly MRSA surveillance of neonates in the NICU was strongly cost-effective, with ICER values <$10,000/QALY. As excess MRSA attributable stay increased, the economic value of surveillance also increased.

3.4.2 *Number Needed to Screen to Prevent One MRSA Case*

The primary model outcomes measure was the number of neonates needed to screen on a weekly basis for the duration of their stay to prevent a single MRSA case in the NICU. We estimated the number needed to screen (NNS) for varying annual MRSA incidence and contact isolation efficacy. As the annual MRSA incidence increased, the NNS decreased. When R=0.5, annual MRSA incidence was 2.5%, and there was 50% isolation efficacy in preventing secondary cases of MRSA, 102 neonates would need to have weekly surveillance cultures to prevent a single MRSA case. Increasing contact isolation efficacy to 75% for the same scenario would decrease the NNS to 66 neonates. Similarly, if a hospital had a 5% annual MRSA incidence rate, R=0.5, and 75% isolation efficacy, then only 33 neonates would need to be screened to prevent a MRSA case. Figure 3.2 outlines how NNS screen to prevent one infection (Figure 3.2a) and one case of MRSA (Figure 3.2b) varied by annual MRSA incidence rates and contact isolation efficacies when R=0.5.

3.4.3 *Cost Per MRSA Case Averted*

We also calculated the cost per MRSA case averted with the implementation of surveillance and increased contact precautions in the NICU for varying annual MRSA incidence, R, and contact isolation efficacy. When annual MRSA incidence was low (1%) and the efficacy of contact isolation was also relatively low (25%) then the cost per case averted was relatively high, costing $92,175/MRSA case averted. As the efficacy of contact isolation increased to 50%, the associated cost per case averted substantially decreased to $46,942/ MRSA case. Further, as the efficacy of contact isolation increased to 75% the cost per case averted decreased to $30,264.

This trend was consistent across annual MRSA incidence rates, as can be seen on Figure 3.3a which outlines the cost per MRSA infection averted and 3.3b outlining the cost per MRSA case (infection or colonization) averted for varying MRSA incidence and contact isolation efficacy, when R=0.5. Lower costs per case averted are a better economic value.

3.4.4 *ICER Values*

For all scenarios tested the ICER values were <$10,000, representing a cost-effective intervention. Similar to the number needed to treat analyses and cost per case averted, the economic value of surveillance increased as the annual MRSA incidence increased. Additionally, as the net reproductive rate increased, the ICER values also decreased, signifying an increased economic value. As long as the efficacy of isolation in preventing secondary MRSA cases in the NICU was≥50%, then th e ICER values were <$5,000/QALY across all tested annual MRSA incidence rates.

3.5 CONCLUSIONS

Our study suggests that active surveillance in the NICU would be an economically valuable intervention across a wide range of scenarios. Debate remains about the economic and health value of MRSA surveillance. Our study suggests that hospitals with moderate to high adherence to increased contact precautions protocols could benefit from the implementation of active surveillance. Vertical transmission of *S. aureus* is relative rare, which suggests that the majority of MRSA cases in the NICU are the result of preventable instances of horizontal

transmission.[140] Hospitals ought to consider adding active surveillance for MRSA to a suite of NICU infection control precautions as an effective measure for preventing excess morbidity and mortality. Hospitals with a high annual MRSA incidence can prevent a substantial number of nosocomial infections with active surveillance and isolation. Those facilities with a lower annual MRSA incidence and moderate adherence to increased contact precautions (≥50% efficacy) can also benefit by preventing nosocomial MRSA cases.

Hospitals with large NICUs and moderate to high adherence (≥50% efficacy) to utilizing contact precautions should implement weekly surveillance in their facilities to prevent neonatal morbidity and mortality. Outbreaks of MRSA in the NICU could be prevented if routine surveillance were implemented to identify and isolate asymptomatic carriers. Monoclonal outbreaks, such as the outbreak that occurred at University of Bonn Hospital, Bonn, Germany from November 2005 to January 2006, could be prevented with routine surveillance and heightened infection control practices.[141] In this hospital, before the outbreak routine MRSA surveillance was not utilized by infection control personnel. However, serial surveillance of the nares, throat, axilla, anus, groin, and stool was successfully utilized as an infection control strategy that was able to halt the outbreak when neonates who tested positive were decolonized. Further, these investigators advocate the utilization of routine screening and decolonization and/or exclusion of healthcare workers in the NICU who may be persistent carriers of MRSA. Routine screening strategies have been key components of outbreak containment programs. Hospitals should strongly consider implementing NICU screening as a routine infection prevention program.

In addition to the University of Bonn Hospital outbreak, numerous outbreaks of MRSA in the NICU have been reported globally. Often these outbreaks have significant morbidity and

mortality that may have been prevented with increased contact precautions, especially among asymptomatically colonized neonates.[5, 41-42, 129-130, 133-134, 136, 142] Asymptomatic neonates can be colonized with *S. aureus* on their skin, umbilicus, nares, and perineum. Systematic decolonization of all neonates in the NICU as an outbreak control measure has led to mupirocin resistance.[38] Aggressive contact isolation protocols can also interrupt transmission of MRSA in the NICU without applying the selective pressure that has been documented to induce mupirocin resistance in the NICU. Hospital infection control personnel ought to consider implementing weekly NICU surveillance as a MRSA prevention measure.

3.5.1 *Limitations*

Our model evaluated routine active surveillance and increased contact precautions for positive neonates. We did not evaluate the potential impact of decolonization on surveillance positive neonates. Our study focused on surveillance of only the newborns, not the medical staff in the NICU. Finally, we evaluated only the most common MRSA sequelae in neonates (SSTIs, conjunctivitis, and bacteremia) and did not evaluate more rare MRSA infections.

3.5.2 *Conclusions and Future Directions*

Our results showed that performing MRSA surveillance in the NICU is a cost-effective strategy for a wide range of local MRSA conditions. Our model provides benchmarks of local epidemiological conditions that assist physicians, hospital administrators, and policy makers make decisions about whether to implement surveillance at their hospitals. Despite the upfront costs of performing MRSA surveillance, timely implementation of increased contact precautions

may prevent a significant number of MRSA cases among neonates. Systematic mupirocin application for all neonates during outbreaks has induced mupirocin resistances, limiting future treatment options. With an increasing number of state and local governments requiring surveillance of all patients in high risk units or intensive care units, understanding the potential economic value and preventable disease burden will allow for informed public health policy.

3.6 FIGURES AND TABLES

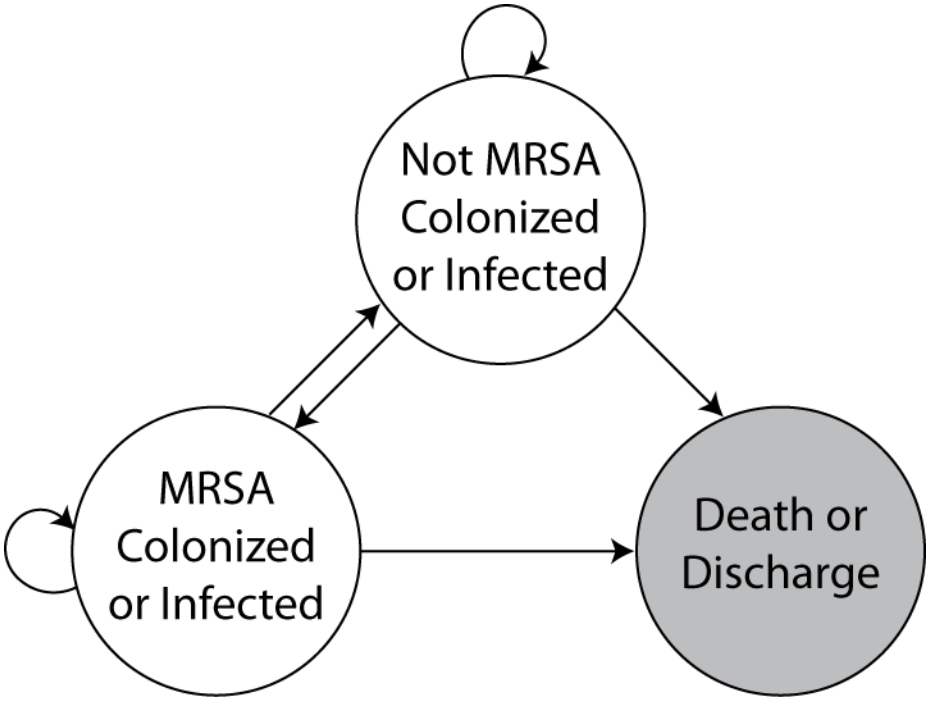

Figure 3.1a: Markov States

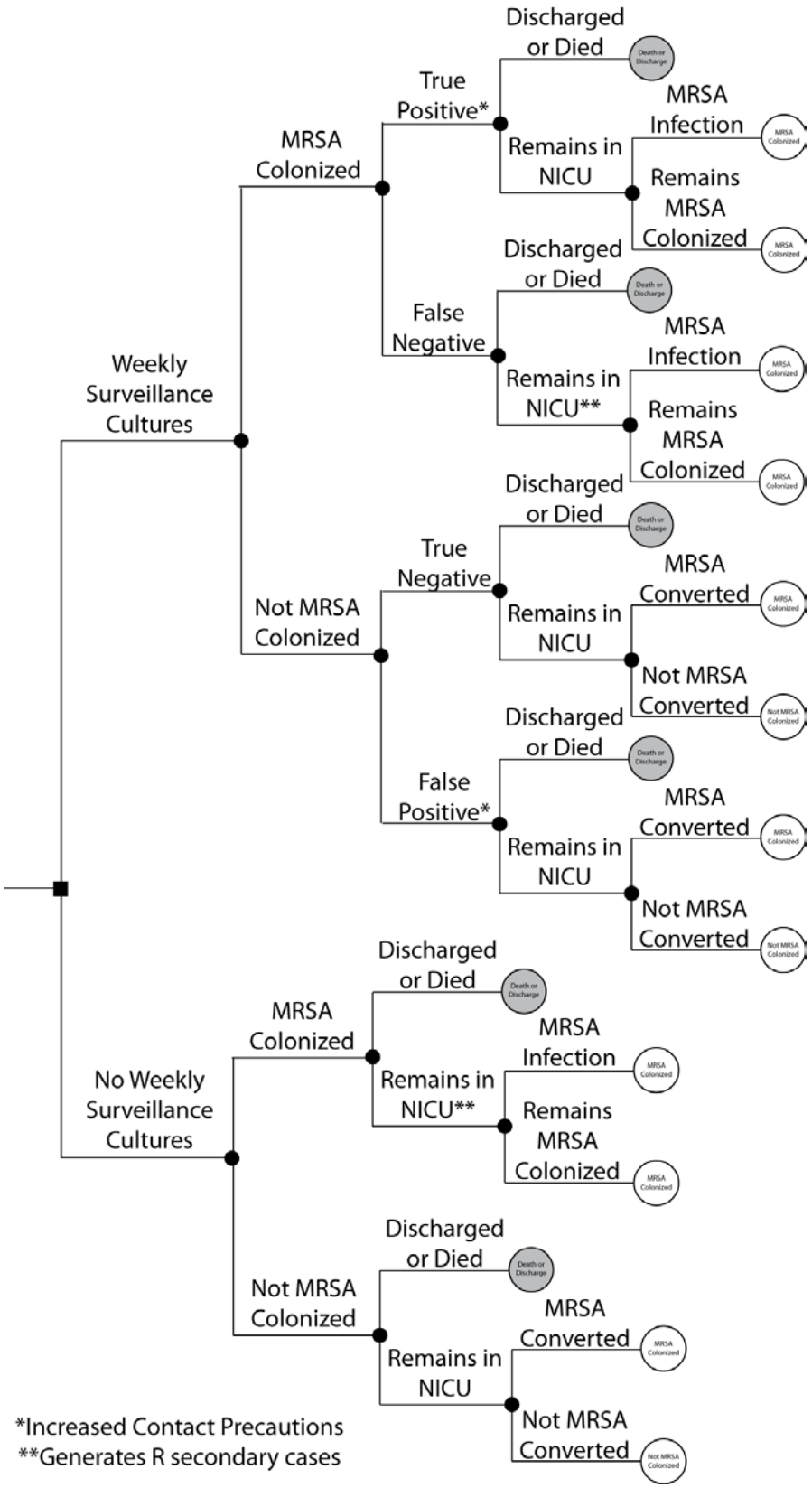

Figure 3.1b: Model Structure

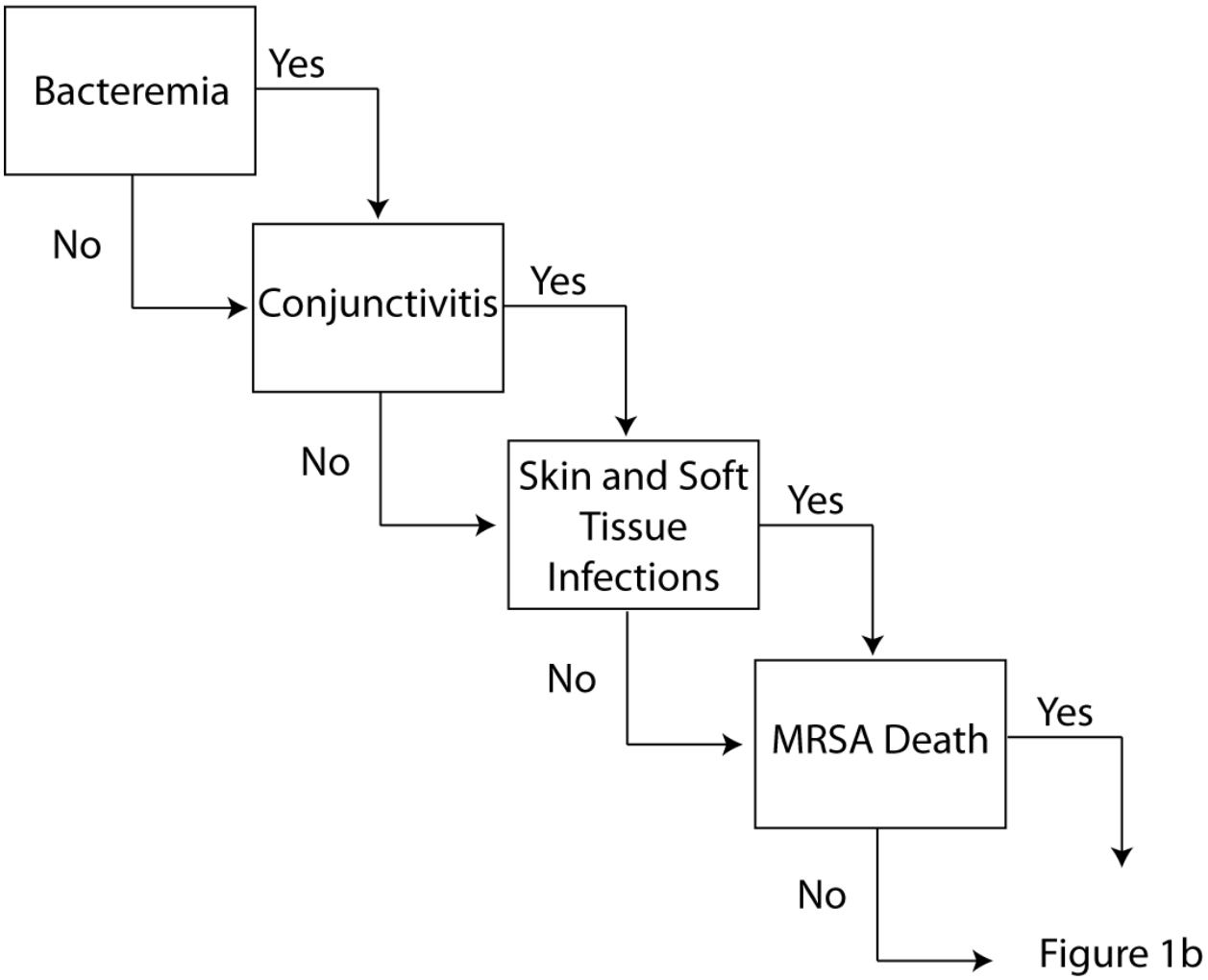

Figure 3.1c: MRSA Infection Outcomes

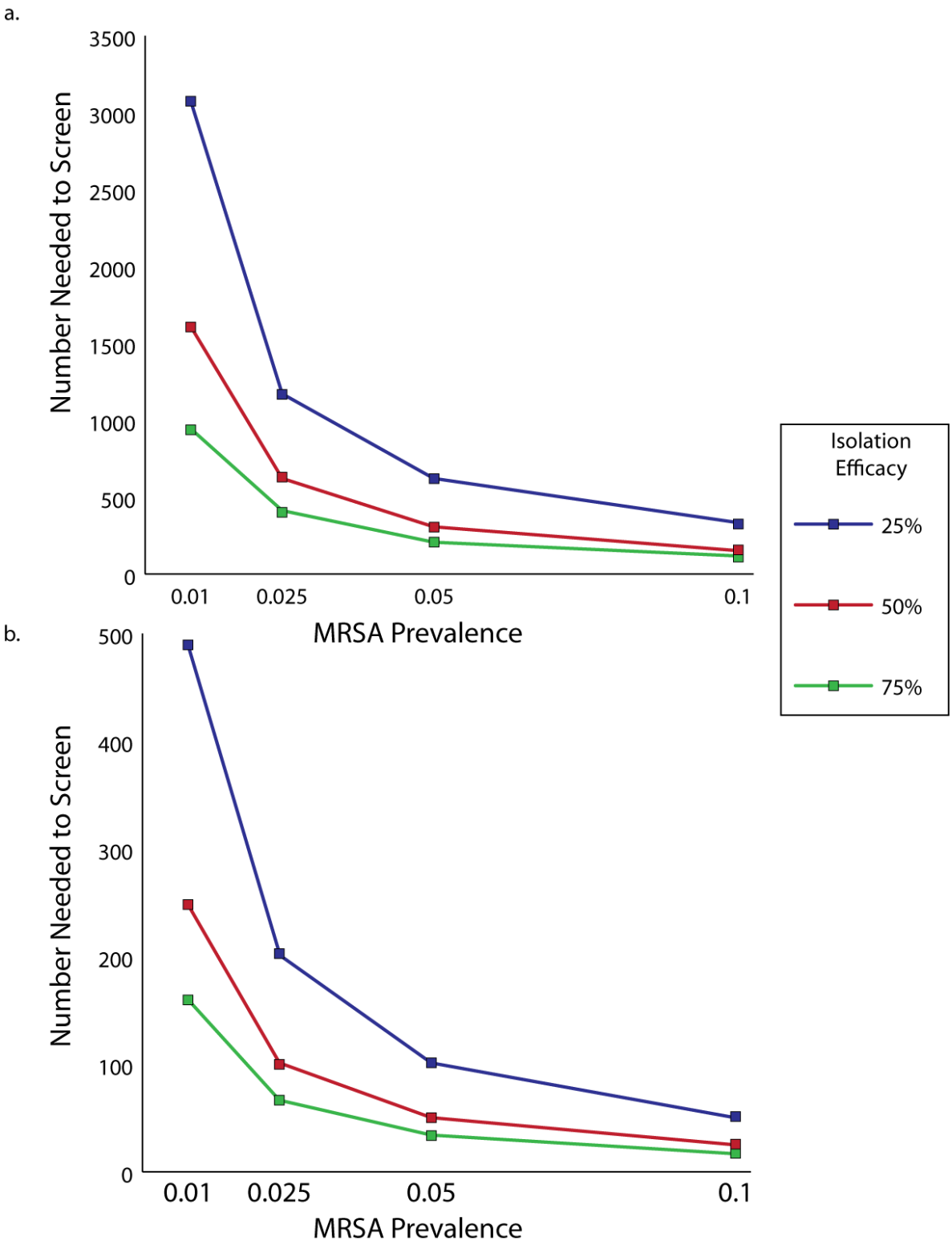

Figure 3.2: Number of neonates needed to screen to prevent one MRSA infection (a.) and one MRSA case (b.) for varying annual MRSA incidence and isolation efficacy, given R=0.5

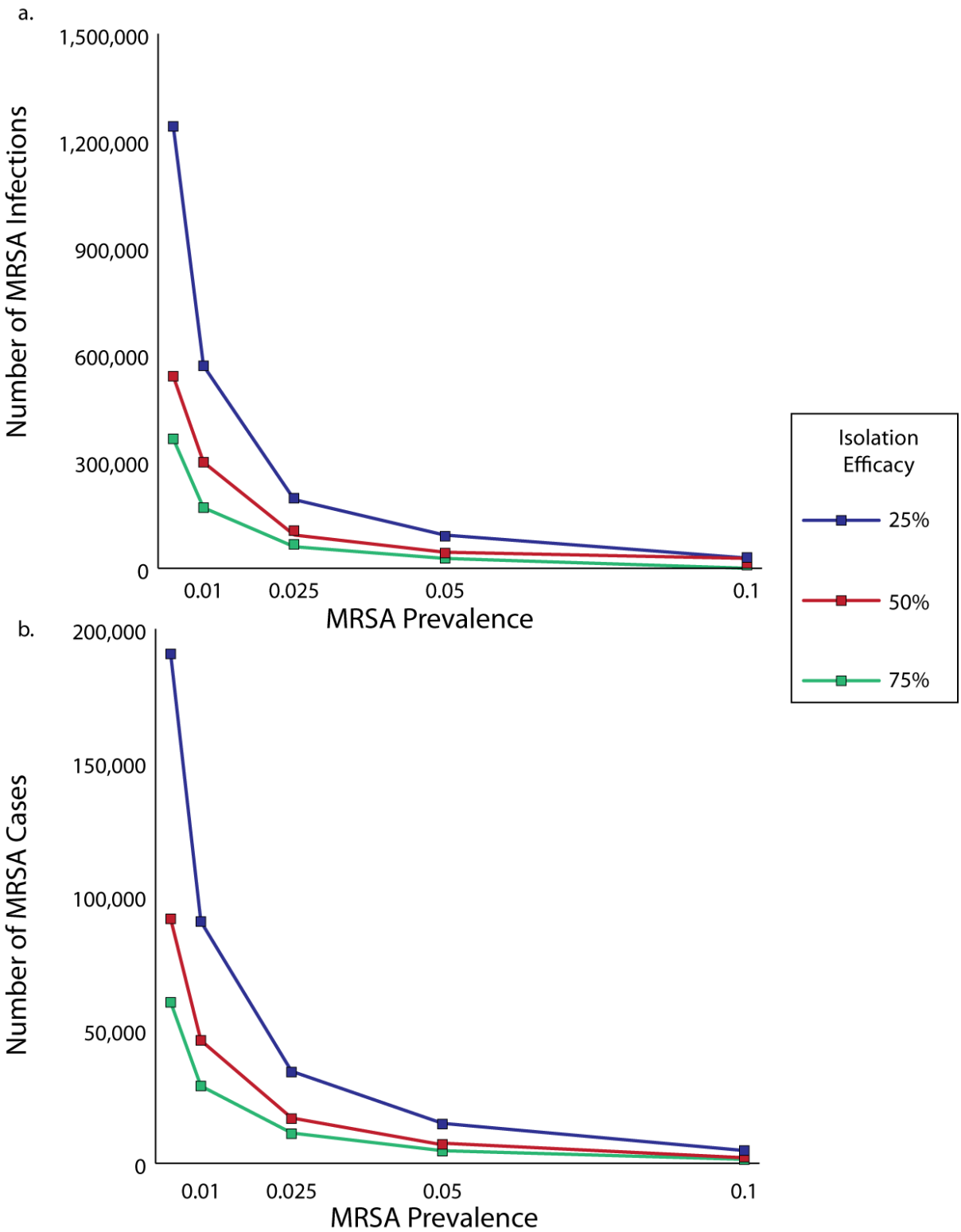

Figure 3.3: Cost per MRSA infection (a.) and MRSA case (b.) averted for varying annual MRSA incidence and isolation efficacy, given R=0.5

Table 3.1: Model Parameters and Sources

Description	Mean	Range		Distribution	Source
		Lower Limit	Upper Limit		
Costs (2010 USD)					
Increased Contact Precautions					
Per Patient Contact					
Gloves	$0.09	--	--	--	[143]
Gowns	$0.92	--	--	--	[143]
Hand Hygiene	$0.12	--	--	--	[143]
Nurse Time to Don Contact Precautions, Minutes	1.0	--	--	--	[143]
Hourly Nurse Wage	$30.65	$21.14	$45.05	Triangular	[144]
Patient Contacts Per Day	78	--	--	--	[145]
Procedures					
Bacteremia					
Blood Culture	$14.79	--	--	--	[33]
Complete Blood Count, Automated	$9.27	--	--	--	[33]
Conjunctivitis					
Bacterial Culture	$12.34	--	--	--	[33]
Blood Culture with White Blood Cell Count	$4.93	--	--	--	[33]
Nasal Smear	$6.80	--	--	--	[33]
Skin & Soft Tissue Infection (SSTI)					
Bacterial Culture	$12.34	--	--	--	[33]
Blood Culture	$14.79	--	--	--	[33]
Incision and Drainage	$487.95	--	--	--	[146]
Hospitalization					
Bacteremia	$5,750	$5,042	$6,457	Gamma	[146]
Conjunctivitis	$3,191	$2,915	$3,468	Gamma	[146]
Skin & Soft Tissue Infection (SSTI)	$3,586	$3,434	$3,740	Gamma	[146]
Mortality, All Causes	$7,129	$5,347	$9,296	Triangular	[147]
Antibiotics					
Trimethoprim/polymyxin eye drops (10mL)	$28.01	$3.52	$81.55	Gamma	[148]
Vancomycin, (10 mg/kg)	$0.84	--	--	--	[148]
MRSA Surveillance					
Agar Surveillance	$12.34	--	--	--	[33]
Polymerase Chain Reaction (PCR)	$50.27	--	--	--	[33]
Nasal Swab	$2.19	--	--	--	[33]

Table 3.1 continued					
Probabilities (%)					
Clinical MRSA Infection†	16	2*	--	Beta	5, 42, 62, 134, 136, 139
Bacteremia†	46	21*	--	Beta	5, 42, 62, 134, 136, 138-139, 149
Conjunctivitis†	40	13*	--	Beta	5, 42, 136
Soft tissue infection†	31	16*	--	Beta	5, 42, 62, 134, 138-139, 149
MRSA Mortality†	19	13*	--	Beta	149-152
Weekly Mortality, All Causes					
Neonates <28 weeks old	0.001115				153
Neonates ≥28 weeks old to 1 year old	0.0000463				153
Effectiveness, Quality-adjusted Life Years (QALYS)					
MRSA Infection‡	0.642	0.24*	--	Beta	
Durations, Days					
Length of Stay, With MRSA	64	35	109	Triangular	138
Length of Stay, With MSSA	64	40	113	Triangular	138

* Standard Deviation

†Given a clinical MRSA infection.

‡Decrement assumed to persist one week.

4.0 THE ECONOMIC VALUE OF DISPENSING HOME-BASED PREOPERATIVE CHLORHEXIDINE BATHING CLOTHS TO PREVENT SURGICAL SITE INFECTIONS

4.1 ABSTRACT

To estimate the economic value of dispensing preoperative home-based chlorhexidine bathing cloth kits to orthopedic patients to prevent surgical site infections (SSIs), a stochastic decision analysis computer simulation model was developed from the hospital's perspective depicting the decision of whether to dispense the kits preoperatively to orthopedic patients. We varied patient age, kit cost, SSI attributable excess length of stay, cost per bed day, patient compliance with the regimen, and cloth antimicrobial efficacy to determine which variables were the most significant drivers to the model's outcomes. When all other variables remained at baseline and cloth efficacy≥50%, patient compliance only had to be half of baseline (baseline mean: 15.3%, range 8.23-20.0%) for the chlorhexidine cloth strategy to be less costly and provide better health outcomes. When cloth efficacy fell to 10%, 1.5 times the baseline bathing compliance, the preoperative bath was also less costly and had better health outcomes. Our study favors the routine distribution of bathing kits. Even with low patient compliance and cloth efficacy values, distribution of bathing kits is an economically beneficial strategy for the prevention of SSIs.

4.2 INTRODUCTION

Surgical site infections (SSIs) are a substantial problem in the United States. Of 46 million surgeries performed annually, at least 1 in every 100 procedures is complicated by a SSI during the hospital stay.[154] These infections are often associated with higher morbidity and mortality rates as well as increased lengths of stay. In 2002, there were approximately 1.7 million SSI cases, resulting in 99,000 deaths.[155] The economic burden associated with these preventable morbidity and mortality rates is high, and a reduction in these values would be advantageous for healthcare facilities. [155-156] It is increasingly important that hospitals adopt preventive measures to increase the safety of their patients and reduce the high costs associated with these infections.

Antiseptic bathing is one of the preoperative procedures recommended by the Centers for Disease Control and Prevention (CDC).[157] Previous studies have shown that screening surgical patients for S*taphylococcus aureus* and selectively decolonizing those who test positive with a regimen including chlorhexidine baths is a cost-effective strategy.[55-56] However, it remains unclear whether to routinely provide preoperative antiseptic bathing to all patients. Low patient compliance rates coupled with varying antimicrobial efficacy reported in recent studies have limited adoption of this prevention technique [written personal communication with Aaron Johnson, MD on 05/10].[158-161]

Our study focuses on the use of home-based patient applied chlorhexidine cloths because recent studies have shown them to be the optimal antiseptic agent for the preoperative bathing of orthopedic patients.[160-161] Unlike other available antiseptic agents (i.e., alcohol and povidone-iodine), chlorhexidine is relatively odorless and colorless, which results in higher observed compliance values. It is also inflammable, making it safer for use in the operating room, and it exhibits greater antibacterial power.[16, 54, 80, 157, 162] Preoperative chlorhexidine rinse is available

both as a liquid soap as well as a saturated polyester cloth, with recent studies noting increased use of the polyester cloth over the liquid soap. Despite past reviews, which have deemed chlorhexidine bathing an unnecessary preoperative procedure, the results from recent clinical trials have been favorable [written personal communication with Aaron Johnson, MD on 05/10].[158-161]

Previous epidemiological studies evaluated the impact of distributing preoperative bathing kits in patients undergoing either knee or hip arthroplasty. This prospective study distributed preoperative bathing kits to 1,054 patients undergoing hip arthroplasty at Sinai Hospital of Baltimore from January 1, 2007 through December 31, 2008.[160] These patients had a mean age of 58 years old (range: 16-89). Analyses were stratified by both risk level of the surgery (low, medium, and high risk) and surgeon (1-4). Baseline incidence of SSIs in this facility was 0.4% for low risk, 2.4% for medium risk, and 5.2% for high risk patients. Among the 4 surgeons at Sinai Hospital of Baltimore, the baseline incidence stratified by surgeon varied from 0.2-4.8%. Among those who were compliant with home-based preoperative bathing there were no incident surgical site infections. These investigators also performed a study distributing the home-based bathing kits to preoperative knee arthroplasty patients at the same hospital.[161] There were 847 patients in the study with a mean patient age 63 years old (range 20-90 years old) included in the study. Among the 136 patients who were compliant in applying the preoperative bathing, there were no surgical site infections compared to 21 infections among the 711 noncompliant individuals (3.0%). These studies both provided proof-of-concept data for the new non-woven preoperative bathing kits. However, they may have been underpowered given the relatively small sample of patients who chose to participate in the bathing program. In the

absence of better powered trials computational modeling can aid in delineating the potential epidemiologic and economic value of implementing preoperative home-based bathing.

We designed a computer simulation model to determine the economic value from the perspective of the hospital of preoperative chlorhexidine bathing for orthopedic patients with polyester cloths. A variety of sensitivity analyses evaluated how varying patient compliance, patient age, chlorhexidine cloth efficacy (i.e., the accompanying decrease in probability of post-operative surgical site infection with preoperative home-based bathing), excess length of stay attributable to SSI and costs influence the cost-effectiveness of the bathing strategy.

4.3 METHODS

Using TreeAge Pro 2009 (TreeAge Software Inc., Williamstown, MA), we developed a stochastic decision analytic computer simulation model depicting the decision of whether or not to distribute a chlorhexidine cloth kit to patients for home-based preoperative bathing (Figure 4.1) in addition to standard in-hospital preoperative preparation. The model evaluated the effects of the distribution of preoperative chlorhexidine bathing kits for the prevention of SSI for patients undergoing orthopedic (hip and knee) surgery. Preoperative bathing refers to the application of the chlorhexidine cloths the evening before and the morning of the surgical procedure. Each kit contains twelve cloths; six cloths each for two preoperative baths that include the disinfection of a patient's head, abdomen, arms, legs, back, and surgical site.[160-161] In-hospital preoperative procedures included preoperative antibiotic prophylaxis with infusion beginning 60 minutes prior to incision of either 1-2g intravenous cefazolin or 1.5g intravenous cefuroxime or 1g intravenous vancomycin. Additionally, surgical site preparation was with a

combination iodine poyacrylaex/alcohol preparation (DuraPrep® solution, 3M: St. Paul, Minnesota) and were standardized in both study populations.[160-161] Postoperative procedures were also standardized among both the intervention and no intervention groups and have been described in detail in previous studies.[160-161]

The model assumed the hospital perspective (i.e. the costs and health benefits experienced by the hospital) and simulated the possible cost-effectiveness of chlorhexidine cloth use under a range of conditions (varying patient age, cloth cost, cost per bed day, SSI attributable length of stay, patient compliance, and cloth antimicrobial efficacy). The hospital perspective includes only the inpatient costs associated with a surgical site infection including excess length of stay, antibiotics, isolation expenses, and physician and nurse time. Lost wages, travel expenses, and outpatient treatments are not included for analyses from the hospital perspective.[11] Outcomes were dependent upon the increased length of stay for patients who acquired an SSI and included only costs associated with this increase to provide an appropriate monetary valuation of the cost of SSIs.[154] A patient's risk of infection after surgery was dependent on SSI risk, cloth efficacy, and compliance data compiled from two similar studies [written personal communication with Aaron Johnson, MD on 05/10].[160-161]

Each simulation run sent 1,000 orthopedic patients through the model 1,000 times for a total of 1,000,000 trials. Each patient was 63 years of age and healthy when entering the model, the median age of an individual undergoing orthopedic surgery. As each patient traveled through the model, he/she had the chance of accumulating costs and quality-adjusted life-years (QALYs) associated with the path he/she traveled. A healthy individual age 0-17 accrues 1 QALY per year. Individuals ages 18-64 can accrue a maximum of 0.92 QALYs during a healthy year, while those ≥65 years old accrue 0.84 QALYs during a healthy year.[128] After all of the patients ran

through the model, the costs and QALY values of the 1,000,000 trials were combined, and an average was computed for the simulation.

For each simulation run, an incremental cost-effectiveness ratio (ICER) was used to calculate the added cost of maintaining a quality-adjusted life-year. The following equation calculates the ICER of employing chlorhexidine cloths as a preoperative technique to prevent SSIs:

$$\text{ICER} = (\text{Cost}_{\text{Chlorhexidine Cloth}} - \text{Cost}_{\text{No Cloth}})/$$

$$(\text{Effectivness}_{\text{ Chlorhexidine Cloth}} - \text{Effectiveness}_{\text{No Cloth}})$$

ICER values below $50,000/QALY were considered relatively cost-effective, and those above the threshold were not considered cost-effective.[163] When the preoperative chlorhexidine cloth intervention is both less costly and provides better health outcomes than that of no intervention, it is known as the dominant strategy, i.e. there is no cost or health effect disadvantage in implementation. Likewise, when the chlorhexidine cloths are more costly and less effective than that of no cloth application, it is considered to be the dominated approach and implementation is discouraged.

Table 4.1 lists the costs, probabilities, time intervals, and effectiveness values used as inputs for our preoperative chlorhexidine bath model as well as corresponding distributions and data sources. All input parameters assume triangular distributions, except the cost of the chlorhexidine cloths used for bathing, which assumes a gamma distribution. Triangular distributions are used when there is limited existing data, such as skewed confidence intervals with an upper and lower bound and resemble the shape of a triangle. Gamma distributions are used to account for variables with skewed distributions, such as costs.[164] Using ICD-9 code

81.54 for total knee replacement, hospital costs were extracted from the healthcare utilization project's (HCUP) national inpatient survey; the cost per bed day was $4,771.[146] Average wholesale cost of the chlorhexidine cloths was systematically determined using various online sources from which a mean and standard deviation were calculated. A 3% discount rate converted all costs into 2010 U.S. dollars.[165]

Our model measured the effectiveness of a chlorhexidine cloth in quality-adjusted life-years (QALY). Each medical condition caused a QALY decrement, which endured only for the duration of the ailment. Most patients undergoing an orthopedic procedure have an age-adjusted baseline QALY value of 0.84 as a result of older age. After the procedure, patients with SSI have a QALY value of 0.756, accounting for the decreased quality of life for the duration of a surgical site infection. Since all patients traveling through the model undergo the same surgical procedure, the associated QALY decrement value for orthopedic surgical patients was null and would not have affected the model's outcomes.[124, 128] SSIs have a mean duration of 9.5 days, so QALY values represented this fraction of the whole year. The time horizon, or period of time included in each simulation, was one year.

In the model, the following variable definitions were utilized to describe the chlorhexidine cloth intervention. Patient compliance was defined as a patient's probability of applying the preoperative baths are directed by their physician. Only patients who were compliant with the intervention preoperatively had a reduced risk of post-operative surgical site infection. Cloth efficacy was defined as the reduction is relative risk of post-operative surgical site infection compared to no intervention, (i.e., if cloth efficacy was 25%, then a patient had a 1.875% (range: 0.6%-4.875%) probability of surgical site infection). Surgical site infection attributable excess length of stay was the number of additional hospital days that patients with

surgical site infection stayed in the hospital postoperatively compared to patients with the same surgeries who did not acquire surgical site infections.

Sensitivity analyses were conducted in order to determine the impact that varying efficacies and costs would have on the cost-effectiveness of the preoperative procedure. We systematically tested a wide range of chlorhexidine bath efficacies (10%, 25%, 50%, and 75%) and patient compliance rates (0.25*baseline compliance-2.00*baseline compliance) to evaluate variations from the baseline data found on Table 4.1 (mean compliance 15.3%, range 8.32%-20.0%). We ran additional simulations varying patient age (53-63 years old), chlorhexidine cloth costs ($10.00-$100.00), SSI attributable excess length of stay (5 days-15 days), cost per bed day ($3,000-$10,000), and probability of surgical site infection without implementation of the bathing intervention.

4.4 RESULTS

When the model was run at the baseline cost scenario (i.e., mean cost $29.35, standard deviation $7.89), distribution of preoperative bathing kits was the economically dominant strategy when cloth efficacy was≥10% and compliance was ≥1.5x the baseline distribution; ≥25% cloth efficacy and ≥75% the baseline compliance distribution; and ≥50% cloth efficacy and ≥50% the baseline compliance distribution. Chlorhexidine cloth cost, length of stay, patient compliance rates, and cloth efficacy were the most significant drivers to the model's outcomes. Patient age (53-63 years old) and cost per bed day ($3,000-$10,000) did not substantially affect model outcomes and are not presented. When the probability of surgical site infection without implementation of the bathing intervention was ≤0.015 and compliance was equal to the baseline

distribution, distribution of kits was never cost-effective. When the probability of infection was 1.75%, distribution of preoperative bathing kits was the dominant strategy when cloth efficacy was ≥75%. Distribution of bathing kits was also the dominant strategy when the probability of SSI was ≥2.0% and the cloth efficacy was ≥50%.

4.4.1 *Cost of Chlorhexidine Cloths*

Table 4.2 shows the results from our analysis. As the cost of the chlorhexidine cloths was increased from the baseline value to $100, the preoperative cloth became highly cost-ineffective at most compliance values and cloth efficacies. At this relatively high cost, distributing the preoperative bathing kits was the dominant strategy only when cloth efficacy was ≥75% and patient compliance was≥75% of the baseline (mean: 11.48%); cloth efficacy was ≥50% and compliance was at least the baseline distribution (i.e., 15.3% (range: 8.23%-20.0%)); and with cloth efficacy≥25% and twice the baseline compliance rate (mean: 30.6%). When the cost of the cloths was decreased to $10 from the baseline rate of 29.35 (±7.89), preoperative bathing became the dominant strategy for all scenarios with efficacy ≥10% and compliance ≥50% of the baseline (mean: 7.65%). An increase in cloth cost to $50 varied little from baseline results.

4.4.2 *Excess Length of Stay Attributable to SSI*

Table 4.3 shows the results from our analysis. As the excess length of stay attributable to SSI for patients was increased from the baseline value of 9.5 days (range: 7.7-11.7 days) to 15 days, the distribution of preoperative bathing kits became dominant at all patient compliance rates when cloth efficacy was at least 25%. When the duration of excess stay was equal to 15

days and cloth efficacy was 10%, the bathing strategy was dominant as long as patient compliance was at least 75% of the baseline value (mean: 11.48%). When the length of stay for patients was decreased from the baseline value (mean: 9.5 days) to 5 days, the kit distribution became dominant in fewer scenarios, specifically at 25% cloth efficacy. Extending the length of stay from the baseline value to 15 days seemed to have a greater impact on the model's outcomes than did decreasing the length of stay.

4.4.3 *Patient Compliance with Bathing*

Although cost and length of stay affected the model's outcomes, patient compliance rates had the greatest impact on results. At baseline compliance (i.e., 15.3% (range: 8.23%-20.0%)), the chlorhexidine cloth was dominant in all simulated runs, as long as chlorhexidine cloth efficacy was ≥50%. When patient compliance values were reduced to ≥50% of baseline, a mean of 7.65%, and chlorhexidine cloth costs were no greater than $50, the chlorhexidine bathing strategy was dominant, as long as the chlorhexidine cloth efficacy was 50%. Even when patient compliance was lower than 50% of baseline (mean: <7.65%), the bathing strategy continued to be the dominant strategy at high cloth efficacy. When patient compliance was doubled, the chlorhexidine bath strategy was dominant in the simulated runs across the range of sensitivity analysis values, as long as chlorhexidine bath efficacy was ≥25%.

4.4.4 *Avoided Infections*

Figure 4.2 presents a graphical representation of the modeled number of infections avoided per thousand preoperative patients that the cloths are distributed to. At baseline patient

compliance (i.e., 15.3% (range: 8.23%-20.0%)) and 25% chlorhexidine cloth efficacy, 1.28 SSIs were avoided per thousand kits distributed. This increased to 2.26 infections avoided at 50% efficacy. When compliance was half of baseline compliance (mean: 7.65%), the number of SSIs avoided dropped to 1.23 at cloth efficacy of 50%. When patient compliance was double the baseline value and cloth efficacy remained at 50%, the number of infections avoided climbed to 4.7.

4.4.5 *Bath Interventions*

Table 4.4 shows the number of bathing kits that need to be dispensed to prevent one SSI, and Figure 4.3 presents a graphical representation of the data. When cost and length of stay was held at baseline, which for cost was $29.35 (±$7.89) and length of stay was 9.5 days (7.7-11.7 days), the number of kits that need to be distributed to prevent one SSI was calculated. As patient compliance increased, the absolute number of patients who needed to be prescribed a chlorhexidine bathing kit decreased. When compliance was a quarter of baseline (mean: 3.83%), the difference in number of bathing interventions was 5,841. When compliance was doubled from baseline (mean: 40%), the difference dropped to 678.

4.4.6 *Cost-Effectiveness Scatter Plot*

Figure 4.4 shows a cost-effectiveness scatter plot when patient compliance in applying the preoperative bath was the baseline distribution, the bath effectiveness was 90%, and preoperative bath cost was the baseline distribution. Each point represents the average of a thousand trials that were conducted for each modeled individual. Blue dots represent those

individuals who were randomized to the bathing intervention while red dots represent individuals who received only standard preoperative care and did not receive preoperative baths. The cost associated with individuals who received the preoperative bath tended to be higher, but they also tended to have higher effectiveness values.

4.4.7 *Relative Risk of Surgical Site Infections*

Figure 4.5 illustrates the relative risk of surgical site infection versus bathing compliance for various bath efficacy scenarios. As patient compliance increased, the relative of risk of surgical site infection with preoperative bathing decreased. Additionally, as the efficacy of the preoperative bath increased, the relative risk of surgical site infection with preoperative bathing also decreased. When bathing was 75% effacicious in preventing surgical site infections and patient compliance was the baseline distribution (mean: 0.153, range: 0.0823-0.200), the relative risk of SSI was 0.89. Increasing patient compliance to 1.5 times the baseline distribution the realtive risk decreased to 0.83, and as patient compliance increased to 2 times the baseline distribution the relative risk decreased to 0.78.

4.5 DISCUSSION

A recent study estimated that the cost of preventable SSIs in U.S. is estimated to be $166 million to $345 million.[166] Our model demonstrates that home-based preoperative bathing with chlorhexidine impregnated cloths is a cost-effective strategy across a wide range of antimicrobial

efficacy and patient compliance values. The intervention remains cost effective even for fairly low cloth efficacies and patient compliance values. For bathing to remain the economically dominant strategy cloth efficacy can be as low as 10%, as long as patient compliance was doubled from baseline to a mean value from a previous study to 30.60% (range: 16.46%-40.00%). Conversely, patient compliance can be as low as half of the baseline value (i.e., 7.65% (range: 4.16%-10.00%)) as long as cloth efficacy was 75%. The patient compliance/cloth efficacy pair was impetus of the economic value of preoperative chlorhexidine bathing.

To date, most of the opposition to home-based preoperative chlorhexidine bathing has emerged from concerns about low cloth antimicrobial efficacy and patient compliance. However, our study suggests these concerns may not be as crucial as initially thought. Although the Cochrane Collaboration's 2009 systematic review assessing the effectiveness of preoperative bathing suggested that preoperative bathing with chlorhexidine was not an effective measure in the prevention of SSIs; this review did not include studies using a relatively new chlorhexidine cloth application.[158, 161] The non-woven polyester fiber cloth, unlike traditional cotton washcloths, results in higher skin surface concentration of chlorhexidine associated with a greater antimicrobial effect.[159] Since our study assumed that patients would receive other standard SSI prevention (i.e., prophylactic antibiotics, proper hair removal, surgical site preparation, etc.) our results suggest that there is additional value in including the distribution of preoperative home-based bathing kits into the package of surgical site prevention techniques used by surgeons.

A recent study by Kassakian and colleagues evaluated the impact of daily bathing with 2% chlorhexidine gluconate versus bathing with soap and water.[167] This quasi-experimental study evaluated a primary outcome of the incidence of MRSA in non-ICU patients. There were

three distinct study periods: 1. January 1, 2008-December 31, 2008 was the control group of the baseline bathing practice using soap and water. 2. January 1, 2009-January 31, 2009 was the wash-in period that included training for implementing chlorhexidine bathing. 3. February 1, 2009-March 31, 2010 was the experimental period during which all patients were bathed daily with chlorhexidine gluconate impregnated cloths. The rate of MRSA and vancomycin resistant enterococci (VRE) in the control group was 0.57 per 1,000 at risk patient days with 20 total cases, while the intervention group had a lower infection rate of 0.28 per 1,000 at risk patient days (10 cases, P=0.06).[167] Using a Cox proportional hazards regression model, the investigators concluded that chlorhexidine bathing had a 0.36 (95% CI: 0.2-0.8) hazard compared to the reference group of traditional soap and water bathing (P=0.01). This study highlights the potential utility of chlorhexidine bathing as an infection prevention strategy that may be used in addition to preoperative home-based bathing.

4.5.1 *Limitations*

All computer simulation models are simplifications of real life scenarios and cannot represent all possible situations and outcomes. Our data inputs came from existing literature that explored the implementation of the chlorhexidine cloths as a SSI prevention technique and sensitivity analyses was performed to assess the robustness of the results. Additional clinical studies may further explore the impact of home-based preoperative chlorhexidine bathing and could be used to update our model in the future.

4.5.2 *Conclusions*

Surgical site infections have substantial preventable morbidity, mortality, and cost. Our model suggests that routine dispensing of home-based preoperative chlorhexidine bathing would have substantial economic value throughout a wide range of patient compliance levels, cloth efficacies, cloth costs, and SSI attributable lengths of hospital stay. Implementing preoperative home-based bathing could decrease the number of reasonably preventable surgical site infections in the U.S. Our study supports the distribution of chlorhexidine cloths for preoperative bathing; this intervention remains cost-effective over a wide range of cloth efficacy and patient compliance values.

4.6 FIGURES AND TABLES

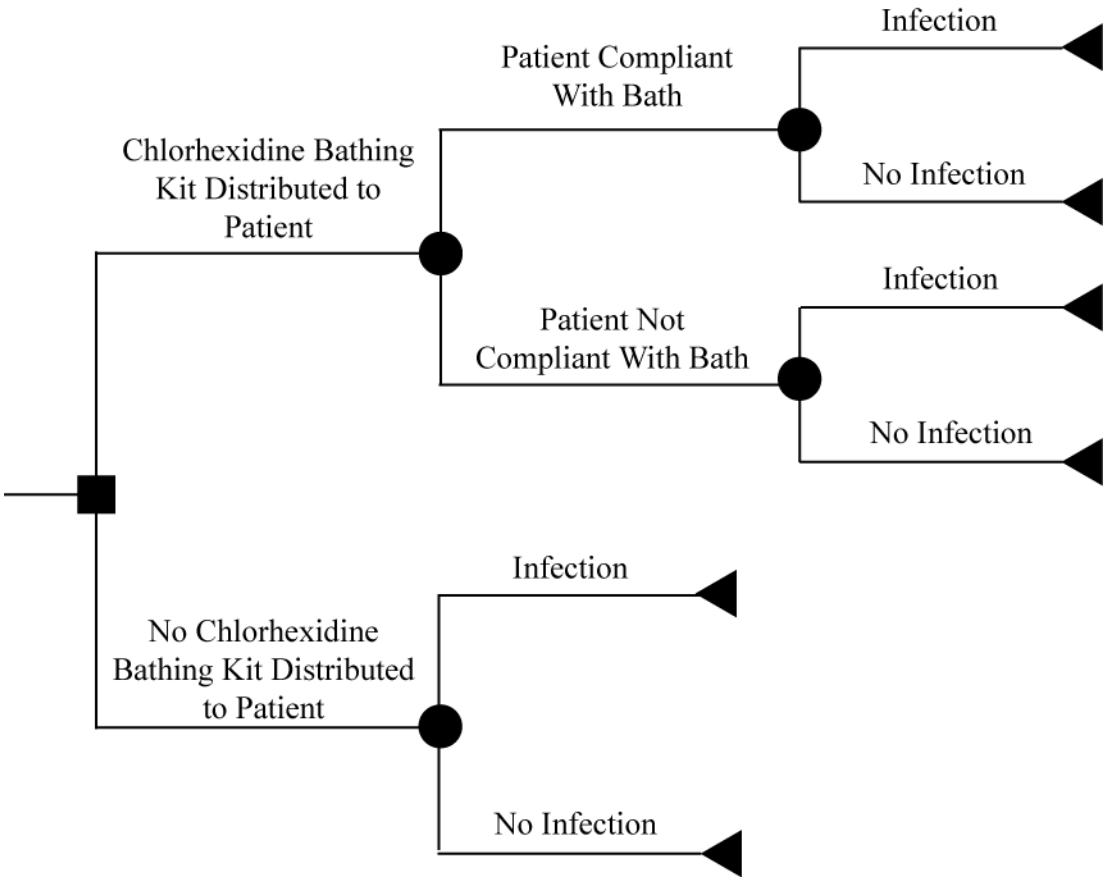

Figure 4.1: Model Structure

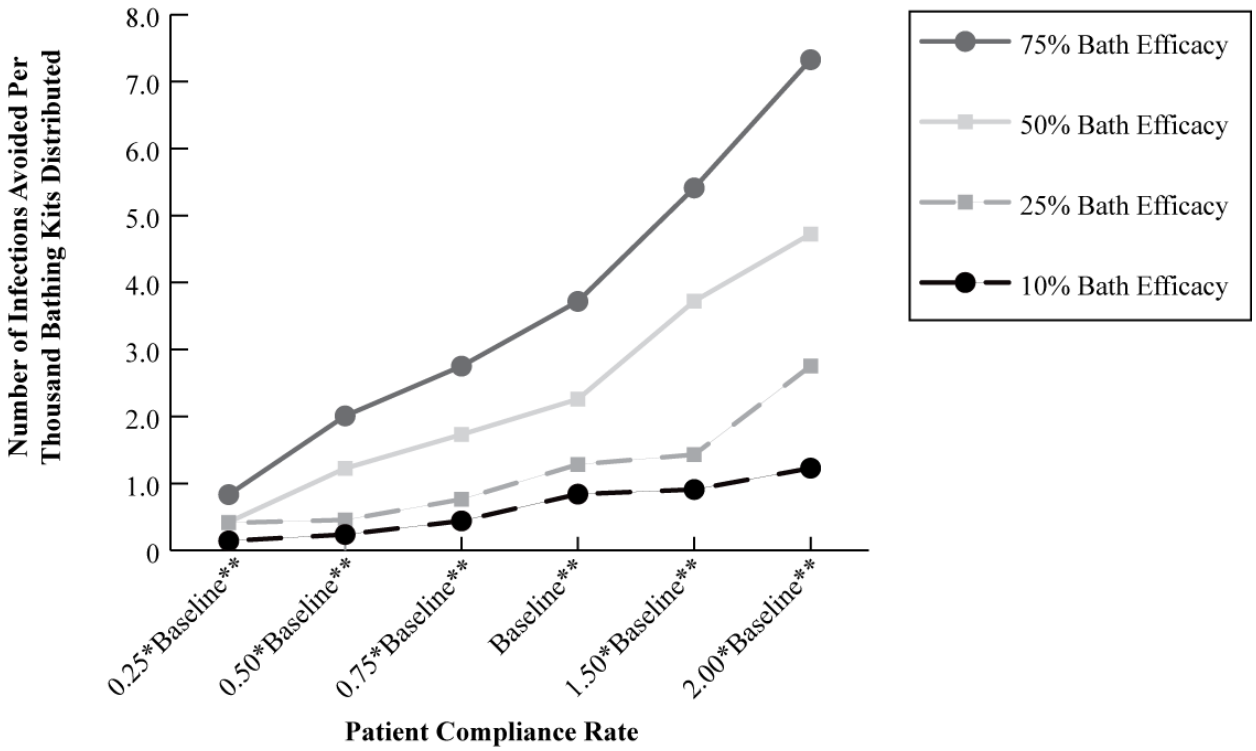

Figure 4.2: Patient Compliance Rate versus Number of Infections Avoided Per Thousand Bathing Kits Distributed

**Baseline Data is a triangular distribution with a mean value of 15.3% and a range of 8.23%-20.0%

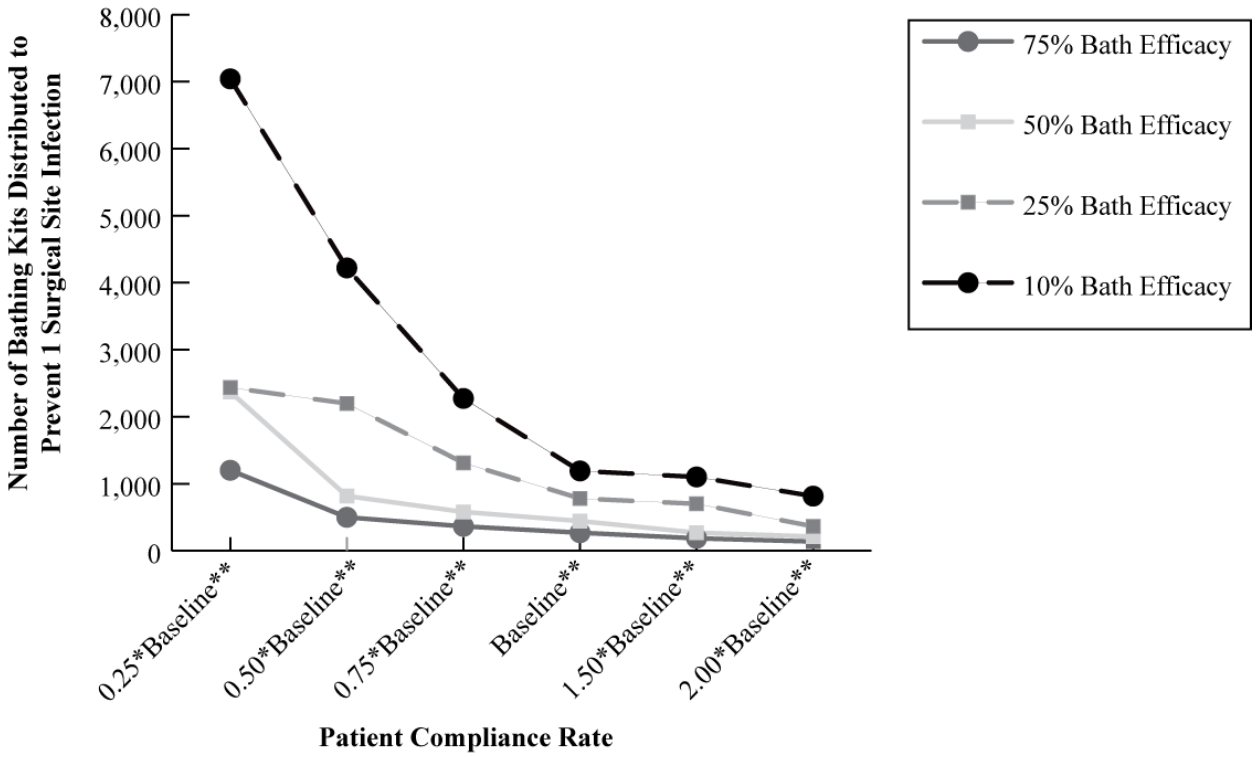

Figure 4.3: Patient Compliance Rate versus Number of Bathing Kits Distributed to Prevent 1 Surgical Site Infection

**Baseline Data is a triangular distribution with a mean value of 15.3% and a range of 8.23%-20.0%

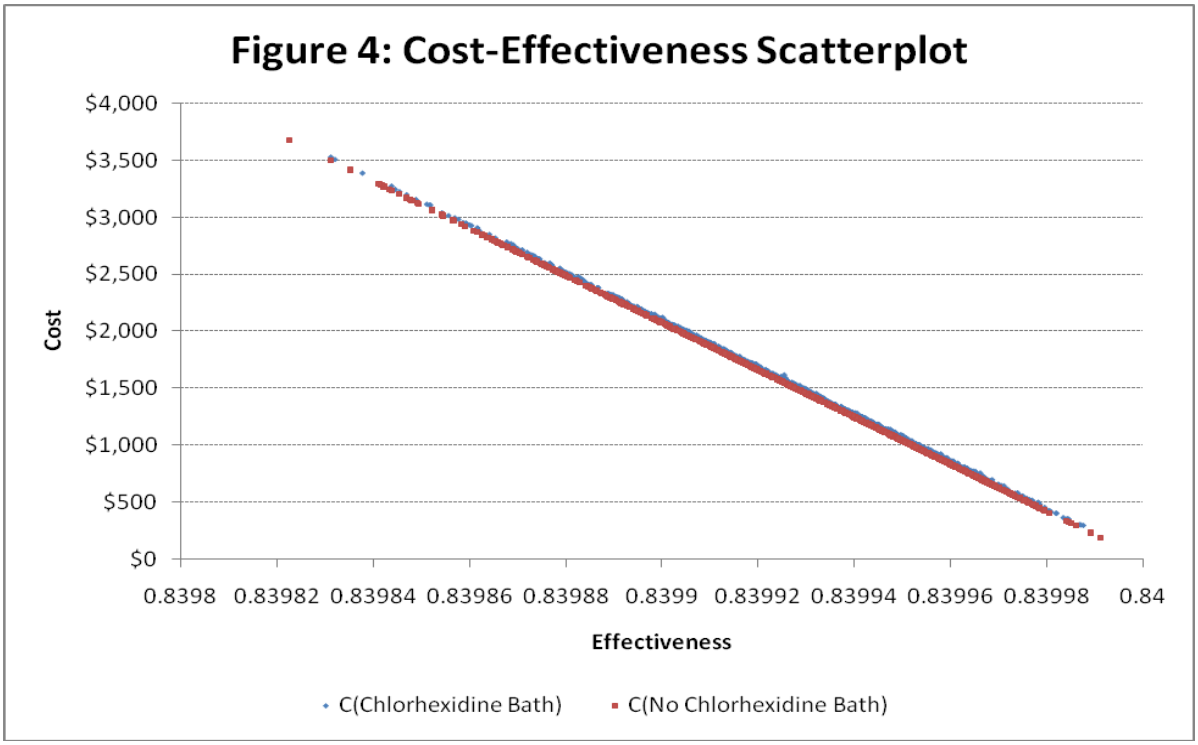

Figure 4.4: Cost-Effectiveness Scatter plot

Each blue dot is a single trial where preoperative chlorhexidine bathing was implemented, and each red dot represents a single trial where preoperative chlorhexidine bathing was not implemented. The y-axis illustrates the ranging costs associated with each trial and the x-axis illustrates the ranging effictveness values, measured in QALYs. Note: in these simulations the difference in QALYs ranged from approximately 0.8398 to 0.84.

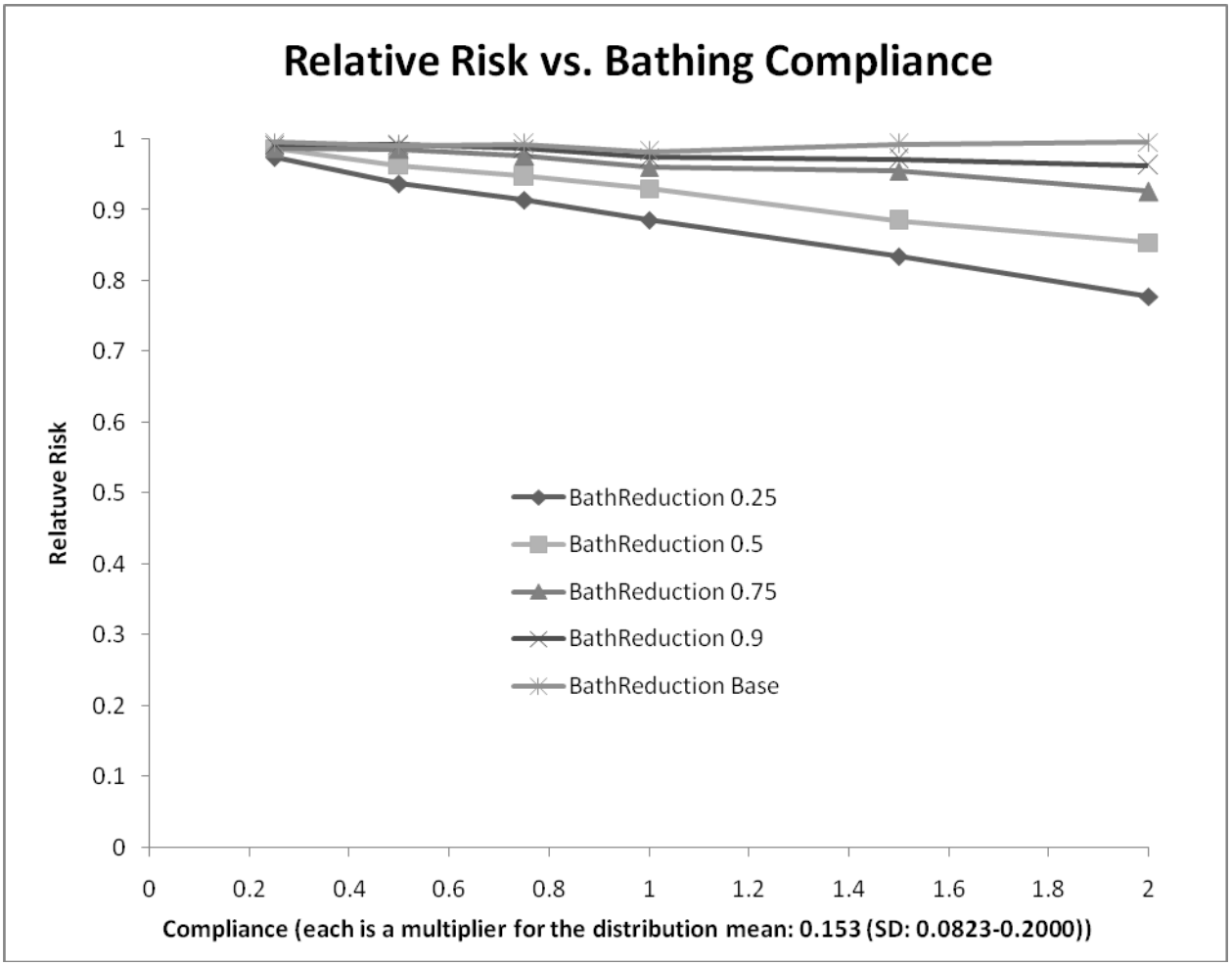

Figure 4.5: Relative Risk of Surgical Site Infection versus Bathing Compliance for Various Bath Efficacy Scenarios

Table 4.1: Model Input Parameters

Description (Units)	Mean	Standard Deviation or Range	Source
Costs ($U.S.)			
Chlorhexidine Wipes	29.35	±7.89	[168-174]
Probabilities			
Compliance	0.153	0.0823 – 0.200	[160-161]
Surgical Site Infection without Bath	0.025	0.008 – 0.065	[160-161]
Time			
Infection (LOS) – Difference	9.5	7.7 – 11.7	[155]
Effectiveness			
Age 63 QALY Value	0.84	-	[128]
Orthopedic SSI QALY Value	0.90	-	[124]

Table 4.2: Cost-Effectiveness of Chlorhexidine Bath based on Cloth Cost					
Cloth Cost	**Compliance Rate†**	**Bath Efficacy in Preventing Surgical Site Infections**			
		10%	***25%***	***50%***	***75%***
	$10.00				
	¼ of Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	½ of Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	¾ of Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	Baseline Cost				
	¼ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	> 1 million[+]
	½ of Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	¾ of Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	$50.00				
	¼ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	> 1 million[+]
	½ of Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	¾ of Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	$100.00				
	¼ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	> 1 million[+]
	½ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	> 1 million[+]
	¾ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	Dominant[*]
	Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]

†Baseline compliance refers to a mean compliance value of 15.3% (range 8.23-20.0%).

> 1 million[+] refers to the model's calculated ICER value. The value is greater than 1 million dollars, which is much greater than the $50,000 cost-effectiveness threshold.[76]

Dominant[*] signifies that the distribution of preoperative bathing kits is dominant over the no bath strategy. It is both less costly and more effective than no preoperative bath.

Table 4.3: Cost-Effectiveness of Chlorhexidine Bath Based on Excess Length of Stay Attributable to Surgical Site Infection

SSI attrib. excess LOS	Compliance Rate†	Bath Efficacy in Preventing Surgical Site Infections			
		10%	***25%***	***50%***	***75%***
5 Days					
	¼ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	> 1 million[+]
	½ of Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	¾ of Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	Baseline Length of Stay				
	¼ of Baseline Compliance	> 1 million[+]	> 1 million[+]	> 1 million[+]	> 1 million[+]
	½ of Baseline Compliance	> 1 million[+]	> 1 million[+]	Dominant[*]	Dominant[*]
	¾ of Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	15 Days				
	¼ of Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	½ of Baseline Compliance	> 1 million[+]	Dominant[*]	Dominant[*]	Dominant[*]
	¾ of Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	1.5x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]
	2x Baseline Compliance	Dominant[*]	Dominant[*]	Dominant[*]	Dominant[*]

†Baseline compliance refers to a mean compliance value of 15.3% (range 8.23-20.0%).

> 1 million[+] refers to the model's calculated ICER value. The value is greater than 1 million dollars, which is much greater than the $50,000 cost-effectiveness threshold.[76]

Dominant[*] signifies that the distribution of preoperative bathing kits is dominant over the no bath strategy. It is both less costly and more effective than no preoperative bath.

Table 4.4: Number of Bathing Kits that Need to be Dispensed to Preoperative Patients to Prevent One Surgical Site Infection

Compliance Rate†	**Bath Efficacy**			
	10%	**25%**	**50%**	**75%**
¼ of Baseline Compliance	7,042	2,434	2,370	1,201
½ of Baseline Compliance	4,220	2,198	817	499
¾ of Baseline Compliance	2,273	1,311	579	364
Baseline Compliance	1,191	780	443	269
1.5x Baseline Compliance	1,101	700	269	185
2x Baseline Compliance	815	364	212	137

†Baseline compliance refers to a mean compliance value of 15.3% (range 8.23-20.0%).

5.0 GENERAL DISCUSSION AND PUBLIC HEALTH IMPORTANCE

Substantial preventable morbidity and mortality due to nosocomial infections occurs each year in the United States and worldwide. The World Health Organization estimates that worldwide daily number of prevalent nosocomial infections is more than 1.4 to 1.7 million.[1, 79] Surveillance and isolation of those who test positive for MRSA can prevent a substantial number of secondary cases of MRSA. With rapid turnaround time, surveillance has the potential to prevent infections and also affords economic benefits. Adding home-based chlorhexidine bathing cloth kits to a suite of pre-operative care for orthopedic patients can surgical site infections and associated mortality.

A multifaceted program of nosocomial infection prevention has the potential to both improve patient outcomes and save third party payers money. Testing adult patients in general medical wards has the potential to prevent nosocomial transmission of MRSA among patients in the hospital. However, policy makers and hospital administrators must carefully consider the attributes of the diagnostic test used in a screening program. Increasing the number of anatomic sites tested with surveillance cultures does not appear to have as great an impact as decreasing turnaround time on the ultimate economic value of a MRSA testing strategy. Hospital infection control personnel could use the models described here to help benchmark the test characteristics to be used in their local infection prevention programs.

Weekly surveillance of all neonates in the NICU and isolation of those who test positive is a second technique that hospitals could use to decrease the incidence on nosocomial infections. Asymptomatic neonates can be colonized with *S. aureus* on their skin, umbilicus, nares, and perineum. When outbreaks of MRSA have occurred in the NICU surveillance has been utilized as a central component of the infection control strategy.[131, 134, 136] Hospitals with moderate to high adherence to isolation protocols have the potential to prevent morbidity and mortality among neonates in the NICU. Understanding the economic and epidemiologic impact of different neonatal MRSA surveillance strategies will help enable decision makers when designing nosocomial infection prevention strategies.

At least 1 in every 100 procedures is complicated by a SSI during their hospital stay, making prevention of postoperative nosocomial infections an area of great promise for decreasing the overall burden of nosocomial infections. Our model evaluated the economic and epidemiologic value of distributing home-based preoperative bathing kits to patients and concluded that the distribution of preoperative bathing kits is cost-effective across a wide range of patient compliance and bath efficacy values. Moreover, the distribution of these kits is economically dominant saving costs and preventing adverse health outcomes for patients postoperatively.

The joint statement issued by the Society for Healthcare Epidemiology of America (SHEA), the Association for Professionals in Infection Control and Epidemiology (ACIP), the Pediatric Infectious Disease Society (PIDS), the Infectious Disease Society of America (IDSA), the Council of State and Territorial Epidemiologists (CSTE), the Association of State and Territorial Health Officials (ASTHO), and the CDC called for the elimination of healthcare associated infections.[68-69] Surveillance and isolation of those who test positive for pathogens

such as MRSA have the potential to eliminate intra-hospital transmission, decreasing morbidity and mortality. Implementation of preoperative care bundles precludes surgical site infections. A multifaceted approach including the surveillance test characteristics, target populations, and interventions modeled here will help move towards the elimination of healthcare acquired infections.

BIBLIOGRAPHY

1. Jarvis WR. Selected aspects of the socioeconomic impact of nosocomial infections: morbidity, mortality, cost, and prevention. Infect Control Hosp Epidemiol 1996;17:552-7.
2. Klevens RM, Edwards JR, Richards CL, Jr., et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007;122:160-6.
3. Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control 2009;37:783-805.
4. Milstone AM, Bryant KA, Huskins WC, Zerr DM. The past, present, and future of healthcare-associated infection prevention in pediatrics: multidrug-resistant organisms. Infect Control Hosp Epidemiol 2010;31 Suppl 1:S18-21.
5. Carey AJ, Della-Latta P, Huard R, et al. Changes in the molecular epidemiological characteristics of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31:613-9.
6. Lee BY, Wiringa AE, Bailey RR, et al. The economic effect of screening orthopedic surgery patients preoperatively for methicillin-resistant Staphylococcus aureus. Infect Control Hosp Epidemiol 2010;31:1130-8.
7. Pop-Vicas A, Mitchell SL, Kandel R, Schreiber R, D'Agata EM. Multidrug-resistant gram-negative bacteria in a long-term care facility: prevalence and risk factors. J Am Geriatr Soc 2008;56:1276-80.
8. Campaign to Prevent Antimicrobial Resistance in Healthcare Settings: Why a Campaign? In. Atlanta, GA: Centers for Disease Control and Prevention; 2001.
9. Chroneou A, Zias N, Beamis JF, Jr., Craven DE. Healthcare-associated pneumonia: principles and emerging concepts on management. Expert Opin Pharmacother 2007;8:3117-31.
10. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clin Infect Dis 2003;36:1418-23.
11. Maragakis LL, Perencevich EN, Cosgrove SE. Clinical and economic burden of antimicrobial resistance. Expert Rev Anti Infect Ther 2008;6:751-63.
12. Graham PL, 3rd, Lin SX, Larson EL. A U.S. population-based survey of Staphylococcus aureus colonization. Ann Intern Med 2006;144:318-25.
13. Gorwitz RJ, Kruszon-Moran D, McAllister SK, et al. Changes in the prevalence of nasal colonization with Staphylococcus aureus in the United States, 2001-2004. J Infect Dis 2008;197:1226-34.
14. Kuehnert MJ, Kruszon-Moran D, Hill HA, et al. Prevalence of Staphylococcus aureus nasal colonization in the United States, 2001-2002. J Infect Dis 2006;193:172-9.

15. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev 1997;10:505-20.
16. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA 2007;298:1763-71.
17. Kallen AJ, Mu Y, Bulens S, et al. Health care-associated invasive MRSA infections, 2005-2008. JAMA 2010;304:641-8.
18. Cooper BS, Stone SP, Kibbler CC, et al. Systematic review of isolation policies in the hospital management of methicillin-resistant Staphylococcus aureus: a review of the literature with epidemiological and economic modelling. Health Technol Assess 2003;7:1-194.
19. Corbella X, Dominguez MA, Pujol M, et al. Staphylococcus aureus nasal carriage as a marker for subsequent staphylococcal infections in intensive care unit patients. Eur J Clin Microbiol Infect Dis 1997;16:351-7.
20. Ellis MW, Hospenthal DR, Dooley DP, Gray PJ, Murray CK. Natural history of community-acquired methicillin-resistant Staphylococcus aureus colonization and infection in soldiers. Clin Infect Dis 2004;39:971-9.
21. Davis KA, Stewart JJ, Crouch HK, Florez CE, Hospenthal DR. Methicillin-resistant Staphylococcus aureus (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. Clin Infect Dis 2004;39:776-82.
22. Garrouste-Orgeas M, Timsit JF, Kallel H, et al. Colonization with methicillin-resistant Staphylococcus aureus in ICU patients: morbidity, mortality, and glycopeptide use. Infect Control Hosp Epidemiol 2001;22:687-92.
23. Huang SS, Platt R. Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization. Clin Infect Dis 2003;36:281-5.
24. Pujol M, Pena C, Pallares R, et al. Nosocomial Staphylococcus aureus bacteremia among nasal carriers of methicillin-resistant and methicillin-susceptible strains. Am J Med 1996;100:509-16.
25. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. Study Group. N Engl J Med 2001;344:11-6.
26. Santos RP, Mayo TW, Siegel JD. Healthcare epidemiology: active surveillance cultures and contact precautions for control of multidrug-resistant organisms: ethical considerations. Clin Infect Dis 2008;47:110-6.
27. Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and enterococcus. Infect Control Hosp Epidemiol 2003;24:362-86.
28. French GL. Methods for screening for methicillin-resistant Staphylococcus aureus carriage. Clin Microbiol Infect 2009;15 Suppl 7:10-6.
29. Tacconelli E. Screening and isolation for infection control. J Hosp Infect 2009;73:371-7.
30. Tacconelli E, De Angelis G, de Waure C, Cataldo MA, La Torre G, Cauda R. Rapid screening tests for meticillin-resistant Staphylococcus aureus at hospital admission: systematic review and meta-analysis. Lancet Infect Dis 2009;9:546-54.
31. Humphreys H, Grundmann H, Skov R, Lucet JC, Cauda R. Prevention and control of methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect 2009;15:120-4.
32. Harbarth S, Hawkey PM, Tenover F, Stefani S, Pantosti A, Struelens MJ. Update on screening and clinical diagnosis of meticillin-resistant Staphylococcus aureus (MRSA). Int J Antimicrob Agents 2010.

33. Centers for Medicare & Medicaid Services. In. Washington, D.C.: U.S. Department of Health and Human Services; 2009.
34. Tacconelli E. Methicillin-resistant Staphylococcus aureus: source control and surveillance organization. Clin Microbiol Infect 2009;15 Suppl 7:31-8.
35. Coates T, Bax R, Coates A. Nasal decolonization of Staphylococcus aureus with mupirocin: strengths, weaknesses and future prospects. J Antimicrob Chemother 2009;64:9-15.
36. Hebert C, Robicsek A. Decolonization therapy in infection control. Curr Opin Infect Dis 2010;23:340-5.
37. McConeghy KW, Mikolich DJ, LaPlante KL. Agents for the decolonization of methicillin-resistant Staphylococcus aureus. Pharmacotherapy 2009;29:263-80.
38. Patel JB, Gorwitz RJ, Jernigan JA. Mupirocin resistance. Clin Infect Dis 2009;49:935-41.
39. Song X, Cheung S, Klontz K, Short B, Campos J, Singh N. A stepwise approach to control an outbreak and ongoing transmission of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit. Am J Infect Control 2010;38:607-11.
40. Schultz ED, Tanaka DT, Goldberg RN, Benjamin DK, Jr., Smith PB. Effect of methicillin-resistant Staphylococcus aureus colonization in the neonatal intensive care unit on total hospital cost. Infect Control Hosp Epidemiol 2009;30:383-5.
41. Bertin ML, Vinski J, Schmitt S, et al. Outbreak of methicillin-resistant Staphylococcus aureus colonization and infection in a neonatal intensive care unit epidemiologically linked to a healthcare worker with chronic otitis. Infect Control Hosp Epidemiol 2006;27:581-5.
42. Khoury J, Jones M, Grim A, Dunne WM, Jr., Fraser V. Eradication of methicillin-resistant Staphylococcus aureus from a neonatal intensive care unit by active surveillance and aggressive infection control measures. Infect Control Hosp Epidemiol 2005;26:616-21.
43. Manzur A, Gudiol F. Methicillin-resistant Staphylococcus aureus in long-term-care facilities. Clin Microbiol Infect 2009;15 Suppl 7:26-30.
44. Coia JE, Duckworth GJ, Edwards DI, et al. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. J Hosp Infect 2006;63 Suppl 1:S1-44.
45. Henderson DK. Managing methicillin-resistant staphylococci: a paradigm for preventing nosocomial transmission of resistant organisms. Am J Med 2006;119:S45-52; discussion S62-70.
46. Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. J Hosp Infect 2010;76:97-102.
47. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control 2007;35:S165-93.
48. Gould DJ, Moralejo D, Drey N, Chudleigh JH. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev 2010:CD005186.
49. Fishman N. Antimicrobial stewardship. Am J Med 2006;119:S53-61; discussion S2-70.
50. Paskovaty A, Pflomm JM, Myke N, Seo SK. A multidisciplinary approach to antimicrobial stewardship: evolution into the 21st century. Int J Antimicrob Agents 2005;25:1-10.
51. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
52. George P, Morris AM. Pro/con debate: Should antimicrobial stewardship programs be adopted universally in the intensive care unit? Crit Care 2010;14:205.

53. Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2005:CD003543.
54. Lee I, Agarwal RK, Lee BY, Fishman NO, Umscheid CA. A Systematic Review and Cost Analysis of Pre-operative Chlorhexidine Skin Antiseptic Versus Iodine for Preventing Surgical Site Infections. Infect Control Hosp Epidemiol 2010.
55. Lee BY, Tsui BY, Bailey RR, et al. Should vascular surgery patients be screened preoperatively for methicillin-resistant Staphylococcus aureus? Infect Control Hosp Epidemiol 2009;30:1158-65.
56. Lee BY, Wiringa AE, Bailey RR, et al. Screening cardiac surgery patients for MRSA: an economic computer model. Am J Manag Care 2010;16:e163-73.
57. Lee BY, Popovich MJ, Tian Y, et al. The potential value of Clostridium difficile vaccine: an economic computer simulation model. Vaccine 2010;28:5245-53.
58. Lee BY, Ufberg PJ, Bailey RR, et al. The potential economic value of a Staphylococcus aureus vaccine for neonates. Vaccine 2010;28:4653-60.
59. Lee BY, Wiringa AE, Bailey RR, Lewis GJ, Feura J, Muder RR. Staphylococcus aureus vaccine for orthopedic patients: an economic model and analysis. Vaccine 2010;28:2465-71.
60. Lee BY, Wettstein ZS, McGlone SM, et al. Economic value of norovirus outbreak control measures in healthcare settings. Clin Microbiol Infect 2010.
61. Allard C, Carignan A, Bergevin M, et al. Secular changes in incidence and mortality associated with Staphylococcus aureus bacteraemia in Quebec, Canada, 1991-2005. Clin Microbiol Infect 2008;14:421-8.
62. Gregory ML, Eichenwald EC, Puopolo KM. Seven-year experience with a surveillance program to reduce methicillin-resistant Staphylococcus aureus colonization in a neonatal intensive care unit. Pediatrics 2009;123:e790-6.
63. Lautenbach E, Nachamkin I, Hu B, et al. Surveillance cultures for detection of methicillin-resistant Staphylococcus aureus: diagnostic yield of anatomic sites and comparison of provider- and patient-collected samples. Infect Control Hosp Epidemiol 2009;30:380-2.
64. Lee BY, Bailey RR, Smith KJ, et al. Universal methicillin-resistant Staphylococcus aureus (MRSA) surveillance for adults at hospital admission: an economic model and analysis. Infect Control Hosp Epidemiol 2010;31:598-606.
65. Nelson RE, Samore MH, Smith KJ, Harbarth S, Rubin MA. Cost-effectiveness of adding decolonization to a surveillance strategy of screening and isolation for methicillin-resistant Staphylococcus aureus carriers. Clin Microbiol Infect 2010;16:1740-6.
66. Brown J, Paladino JA. Impact of rapid methicillin-resistant Staphylococcus aureus polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia: a decision model. Pharmacoeconomics 2010;28:567-75.
67. Murthy A, De Angelis G, Pittet D, Schrenzel J, Uckay I, Harbarth S. Cost-effectiveness of universal MRSA screening on admission to surgery. Clin Microbiol Infect 2010;16:1747-53.
68. Cardo D, Dennehy PH, Halverson P, et al. Moving toward elimination of healthcare-associated infections: a call to action. Am J Infect Control 2010;38:671-5.
69. Cardo D, Dennehy PH, Halverson P, et al. Moving toward elimination of healthcare-associated infections: a call to action. Infect Control Hosp Epidemiol 2010;31:1101-5.
70. Calfee DP, Salgado CD, Classen D, et al. Strategies to prevent transmission of methicillin-resistant Staphylococcus aureus in acute care hospitals. Infect Control Hosp Epidemiol 2008;29 Suppl 1:S62-80.

71. Hardy K, Price C, Szczepura A, et al. Reduction in the rate of methicillin-resistant Staphylococcus aureus acquisition in surgical wards by rapid screening for colonization: a prospective, cross-over study. Clin Microbiol Infect 2010;16:333-9.
72. Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant Staphylococcus aureus at hospital admission and nosocomial infection in surgical patients. Jama 2008;299:1149-57.
73. Filice GA, Nyman JA, Lexau C, et al. Excess costs and utilization associated with methicillin resistance for patients with Staphylococcus aureus infection. Infect Control Hosp Epidemiol 2010;31:365-73.
74. Schulz M, Nonnenmacher C, Mutters R. Cost-effectiveness of rapid MRSA screening in surgical patients. Eur J Clin Microbiol Infect Dis 2009;28:1291-6.
75. Simoens S, Ophals E, Schuermans A. Search and destroy policy for methicillin-resistant Staphylococcus aureus: cost-benefit analysis. J Adv Nurs 2009;65:1853-9.
76. Neumann PJ, Sandberg EA, Bell CM, Stone PW, Chapman RH. Are pharmaceuticals cost-effective? A review of the evidence. Health Aff (Millwood) 2000;19:92-109.
77. Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. J Hosp Infect 1999;43:131-47.
78. Reyes J, Hidalgo M, Diaz L, et al. Characterization of macrolide resistance in Gram-positive cocci from Colombian hospitals: a countrywide surveillance. Int J Infect Dis 2007;11:329-36.
79. WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care is Safer Care. In. Geneva, Switzerland: World Health Organization; 2009.
80. Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clin Microbiol Rev 2004;17:863-93, table of contents.
81. Murthy A, De Angelis G, Pittet D, Schrenzel J, Uckay I, Harbarth S. Cost-effectiveness of universal MRSA screening on admission to surgery. Clin Microbiol Infect 2010.
82. Resch A, Wilke M, Fink C. The cost of resistance: incremental cost of methicillin-resistant Staphylococcus aureus (MRSA) in German hospitals. Eur J Health Econ 2009;10:287-97.
83. Olchanski N, Matthewa C, Fusfeld L, Jarvis WR. Assessment of the Influence of Test Characteristics on the Clinical and Cost Impacts of Methicillin-Resistant *Staphylococcus aureus* Screening Programs in US Hospitals. Infect Control Hosp Epidemiol 2011;32.
84. McCollum M, Sorensen SV, Liu LZ. A comparison of costs and hospital length of stay associated with intravenous/oral linezolid or intravenous vancomycin treatment of complicated skin and soft-tissue infections caused by suspected or confirmed methicillin-resistant Staphylococcus aureus in elderly US patients. Clin Ther 2007;29:469-77.
85. Levit K (Thomson Reuters) SETR, Ryan K (Thomson Reuters), Elixhauser A (AHRQ). HCUP Facts and Figures, 2006: Statistics on Hospital-based Care in the United States. Rockville, MD: Agency for Healthcare Research and Quality 2008.
86. Hermsen ED, Shull SS, Klepser DG, et al. Pharmacoeconomic analysis of microbiologic techniques for differentiating staphylococci directly from blood culture bottles. J Clin Microbiol 2008;46:2924-9.
87. Schwengel DA, McGready J, Berenholtz SM, Kozlowski LJ, Nichols DG, Yaster M. Peripherally inserted central catheters: a randomized, controlled, prospective trial in pediatric surgical patients. Anesth Analg 2004;99:1038-43, table of contents.

88. Valenziano CP, Chattar-Cora D, O'Neill A, Hubli EH, Cudjoe EA. Efficacy of primary wound cultures in long bone open extremity fractures: are they of any value? Arch Orthop Trauma Surg 2002;122:259-61.
89. Lee YL, Cesario T, Gupta G, et al. Surveillance of colonization and infection with Staphylococcus aureus susceptible or resistant to methicillin in a community skilled-nursing facility. Am J Infect Control 1997;25:312-21.
90. Drinka P, Faulks JT, Gauerke C, Goodman B, Stemper M, Reed K. Adverse events associated with methicillin-resistant Staphylococcus aureus in a nursing home. Arch Intern Med 2001;161:2371-7.
91. Hsu RB. Risk factors for nosocomial infective endocarditis in patients with methicillin-resistant Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol 2005;26:654-7.
92. Hsu RB, Chu SH. Impact of methicillin resistance on clinical features and outcomes of infective endocarditis due to Staphylococcus aureus. Am J Med Sci 2004;328:150-5.
93. Jeffres MN, Isakow W, Doherty JA, et al. Predictors of mortality for methicillin-resistant Staphylococcus aureus health-care-associated pneumonia: specific evaluation of vancomycin pharmacokinetic indices. Chest 2006;130:947-55.
94. Wenisch C, Laferl H, Szell M, et al. A holistic approach to MRSA eradication in critically ill patients with MRSA pneumonia. Infection 2006;34:148-54.
95. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. Chest 2003;124:1789-97.
96. Hill EE, Vanderschueren S, Verhaegen J, et al. Risk factors for infective endocarditis and outcome of patients with Staphylococcus aureus bacteremia. Mayo Clin Proc 2007;82:1165-9.
97. Kuo CB, Lin JC, Peng MY, Wang NC, Chang FY. Endocarditis: impact of methicillin-resistant Staphylococcus aureus in hemodialysis patients and community-acquired infection. J Microbiol Immunol Infect 2007;40:317-24.
98. Sherwood M, Smith D, Crisel R, Veledar E, Lerakis S. Staphylococcus aureus endocarditis: The Grady Memorial Hospital Experience. Am J Med Sci 2006;331:84-7.
99. Yoon HJ, Choi JY, Kim CO, Kim JM, Song YG. A comparison of clinical features and mortality among methicillin-resistant and methicillin-sensitive strains of Staphylococcus aureus endocarditis. Yonsei Med J 2005;46:496-502.
100. Lin JC, Yeh KM, Peng MY, Chang FY. Community-acquired methicillin-resistant Staphylococcus aureus bacteremia in Taiwan: risk factors for acquisition, clinical features and outcome. J Microbiol Immunol Infect 2004;37:24-8.
101. Chang FY, MacDonald BB, Peacock JE, Jr., et al. A prospective multicenter study of Staphylococcus aureus bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) 2003;82:322-32.
102. Fleisch F, Zbinden R, Vanoli C, Ruef C. Epidemic spread of a single clone of methicillin-resistant Staphylococcus aureus among injection drug users in Zurich, Switzerland. Clin Infect Dis 2001;32:581-6.
103. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically Ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus. Arch Intern Med 2002;162:2229-35.
104. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005;26:166-74.

105. Libert M, Elkholti M, Massaut J, Karmali R, Mascart G, Cherifi S. Risk factors for meticillin resistance and outcome of Staphylococcus aureus bloodstream infection in a Belgian university hospital. J Hosp Infect 2008;68:17-24.
106. Reed SD, Friedman JY, Engemann JJ, et al. Costs and outcomes among hemodialysis-dependent patients with methicillin-resistant or methicillin-susceptible Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol 2005;26:175-83.
107. Shurland S, Zhan M, Bradham DD, Roghmann MC. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible Staphylococcus aureus. Infect Control Hosp Epidemiol 2007;28:273-9.
108. Wang JL, Chen SY, Wang JT, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant Staphylococcus aureus and methicillin-susceptible S. aureus. Clin Infect Dis 2008;46:799-806.
109. Tacconelli E, Pop-Vicas AE, D'Agata EM. Increased mortality among elderly patients with meticillin-resistant Staphylococcus aureus bacteraemia. J Hosp Infect 2006;64:251-6.
110. Hallin M, Denis O, Deplano A, et al. Evolutionary relationships between sporadic and epidemic strains of healthcare-associated methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect 2008;14:659-69.
111. Cordova SP, Heath CH, McGechie DB, Keil AD, Beers MY, Riley TV. Methicillin-resistant Staphylococcus aureus bacteraemia in Western Australian teaching hospitals, 1997-1999: risk factors, outcomes and implications for management. J Hosp Infect 2004;56:22-8.
112. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis 2003;36:53-9.
113. Greiner W, Rasch A, Kohler D, Salzberger B, Fatkenheuer G, Leidig M. Clinical outcome and costs of nosocomial and community-acquired Staphylococcus aureus bloodstream infection in haemodialysis patients. Clin Microbiol Infect 2007;13:264-8.
114. Wang FD, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteremia. Am J Infect Control 2008;36:118-22.
115. Wyllie DH, Crook DW, Peto TE. Mortality after Staphylococcus aureus bacteraemia in two hospitals in Oxfordshire, 1997-2003: cohort study. BMJ 2006;333:281.
116. David TE, Gavra G, Feindel CM, Regesta T, Armstrong S, Maganti MD. Surgical treatment of active infective endocarditis: a continued challenge. J Thorac Cardiovasc Surg 2007;133:144-9.
117. Gammie JS, O'Brien SM, Griffith BP, Peterson ED. Surgical treatment of mitral valve endocarditis in North America. Ann Thorac Surg 2005;80:2199-204.
118. Murashita T, Sugiki H, Kamikubo Y, Yasuda K. Surgical results for active endocarditis with prosthetic valve replacement: impact of culture-negative endocarditis on early and late outcomes. Eur J Cardiothorac Surg 2004;26:1104-11.
119. Athanassa Z, Siempos, II, Falagas ME. Impact of methicillin resistance on mortality in Staphylococcus aureus VAP: a systematic review. Eur Respir J 2008;31:625-32.
120. DeRyke CA, Lodise TP, Jr., Rybak MJ, McKinnon PS. Epidemiology, treatment, and outcomes of nosocomial bacteremic Staphylococcus aureus pneumonia. Chest 2005;128:1414-22.
121. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to Staphylococcus aureus, 2003-04 influenza season. Emerg Infect Dis 2006;12:894-9.

122. Kollef KE, Reichley RM, Micek ST, Kollef MH. The modified APACHE II score outperforms Curb65 pneumonia severity score as a predictor of 30-day mortality in patients with methicillin-resistant Staphylococcus aureus pneumonia. Chest 2008;133:363-9.
123. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA 2009;301:2362-75.
124. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. Med Care 2000;38:583-637.
125. Selai C, Rosser R. Eliciting EuroQol descriptive data and utility scale values from inpatients. A feasibility study. Pharmacoeconomics 1995;8:147-58.
126. Sackett DL, Torrance GW. The utility of different health states as perceived by the general public. J Chronic Dis 1978;31:697-704.
127. van der Meulen JH, Steyerberg EW, van der Graaf Y, et al. Age thresholds for prophylactic replacement of Bjork-Shiley convexo-concave heart valves. A clinical and economic evaluation. Circulation 1993;88:156-64.
128. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998;36:778-92.
129. Behari P, Englund J, Alcasid G, Garcia-Houchins S, Weber SG. Transmission of methicillin-resistant Staphylococcus aureus to preterm infants through breast milk. Infect Control Hosp Epidemiol 2004;25:778-80.
130. Campbell JR, Zaccaria E, Mason EO, Jr., Baker CJ. Epidemiological analysis defining concurrent outbreaks of Serratia marcescens and methicillin-resistant Staphylococcus aureus in a neonatal intensive-care unit. Infect Control Hosp Epidemiol 1998;19:924-8.
131. Johnson AP, Sharland M, Goodall CM, et al. Enhanced surveillance of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in children in the UK and Ireland. Arch Dis Child 2010;95:781-5.
132. Kikuchi K. Genetic basis of neonatal methicillin-resistant Staphylococcus aureus in Japan. Pediatr Int 2003;45:223-9.
133. Morel AS, Wu F, Della-Latta P, Cronquist A, Rubenstein D, Saiman L. Nosocomial transmission of methicillin-resistant Staphylococcus aureus from a mother to her preterm quadruplet infants. Am J Infect Control 2002;30:170-3.
134. Murillo JL, Cohen M, Kreiswirth B. Results of nasal screening for methicillin-resistant Staphylococcus aureus during a neonatal intensive care unit outbreak. Am J Perinatol 2010;27:79-81.
135. Ng SP, Gomez JM, Lim SH, Ho NK. Reduction of nosocomial infection in a neonatal intensive care unit (NICU). Singapore Med J 1998;39:319-23.
136. Saiman L, Cronquist A, Wu F, et al. An outbreak of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2003;24:317-21.
137. Holt PG, Jones CA. The development of the immune system during pregnancy and early life. Allergy 2000;55:688-97.
138. Carey AJ, Duchon J, Della-Latta P, Saiman L. The epidemiology of methicillin-susceptible and methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit, 2000-2007. J Perinatol 2010;30:135-9.
139. Sarda V, Molloy A, Kadkol S, Janda WM, Hershow R, McGuinn M. Active surveillance for methicillin-resistant Staphylococcus aureus in the neonatal intensive care unit. Infect Control Hosp Epidemiol 2009;30:854-60.

140. Pinter DM, Mandel J, Hulten KG, Minkoff H, Tosi MF. Maternal-infant perinatal transmission of methicillin-resistant and methicillin-sensitive Staphylococcus aureus. Am J Perinatol 2009;26:145-51.
141. Heinrich N, Mueller A, Bartmann P, Simon A, Bierbaum G, Engelhart S. Successful management of an MRSA outbreak in a neonatal intensive care unit. Eur J Clin Microbiol Infect Dis 2011.
142. Gerken MV. An outbreak of methicillin-resistant Staphylococcus aureus in a large medical center. Am Surg 1983;49:179-81.
143. Puzniak LA, Gillespie KN, Leet T, Kollef M, Mundy LM. A cost-benefit analysis of gown use in controlling vancomycin-resistant Enterococcus transmission: is it worth the price? Infect Control Hosp Epidemiol 2004;25:418-24.
144. National Compensation Survey: occupational wages in the United States, June 2006. U.S. Department of Labor, 2007. (Accessed April, 2010, at
145. Cohen B, Saiman L, Cimiotti J, Larson E. Factors associated with hand hygiene practices in two neonatal intensive care units. Pediatr Infect Dis J 2003;22:494-9.
146. Healthcare Cost and Utilization Project. In: U.S. Department of Health and Human Services: Agency for Healthcare Research and Quality; 2010.
147. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. Ann Intern Med 1999;130:789-99.
148. PDR. Redbook. 2010 ed. Montvale, NJ: Thompson Healthcare Inc.; 2010.
149. Gerber SI, Jones RC, Scott MV, et al. Management of outbreaks of methicillin-resistant Staphylococcus aureus infection in the neonatal intensive care unit: a consensus statement. Infect Control Hosp Epidemiol 2006;27:139-45.
150. Isaacs D, Fraser S, Hogg G, Li HY. Staphylococcus aureus infections in Australasian neonatal nurseries. Arch Dis Child Fetal Neonatal Ed 2004;89:F331-5.
151. Chuang YY, Huang YC, Lee CY, Lin TY, Lien R, Chou YH. Methicillin-resistant Staphylococcus aureus bacteraemia in neonatal intensive care units: an analysis of 90 episodes. Acta Paediatr 2004;93:786-90.
152. Kuint J, Barzilai A, Regev-Yochay G, Rubinstein E, Keller N, Maayan-Metzger A. Comparison of community-acquired methicillin-resistant Staphylococcus aureus bacteremia to other staphylococcal species in a neonatal intensive care unit. Eur J Pediatr 2007;166:319-25.
153. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2006 period linked birth/infant death data set. Natl Vital Stat Rep 2010;58:1-31.
154. Graves N, Harbarth S, Beyersmann J, Barnett A, Halton K, Cooper B. Estimating the cost of health care-associated infections: mind your p's and q's. Clin Infect Dis 2010;50:1017-21.
155. de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. Am J Infect Control 2009;37:387-97.
156. Evans RP. Surgical site infection prevention and control: an emerging paradigm. J Bone Joint Surg Am 2009;91 Suppl 6:2-9.
157. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78; quiz 79-80.
158. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. Cochrane Database Syst Rev 2007:CD004985.

159. Edmiston CE, Jr., Krepel CJ, Seabrook GR, Lewis BD, Brown KR, Towne JB. Preoperative shower revisited: can high topical antiseptic levels be achieved on the skin surface before surgical admission? J Am Coll Surg 2008;207:233-9.
160. Johnson AJ, Daley JA, Zywiel MG, Delanois RE, Mont MA. Preoperative Chlorhexidine Preparation and the Incidence of Surgical Site Infections After Hip Arthroplasty. J Arthroplasty 2010.
161. Zywiel MG, Daley JA, Delanois RE, Naziri Q, Johnson AJ, Mont MA. Advance pre-operative chlorhexidine reduces the incidence of surgical site infections in knee arthroplasty. Int Orthop 2010.
162. Garibaldi RA. Prevention of intraoperative wound contamination with chlorhexidine shower and scrub. J Hosp Infect 1988;11 Suppl B:5-9.
163. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146:473-81.
164. Thompson SG, Nixon RM. How sensitive are cost-effectiveness analyses to choice of parametric distributions? Med Decis Making 2005;25:416-23.
165. Shepard DS. Cost-effectiveness in Health and Medicine. By M.R. Gold, J.E Siegel, L.B. Russell, and M.C. Weinstein (eds). New York: Oxford University Press, 1996. J Ment Health Policy Econ 1999;2:91-2.
166. Umscheid CA, Mitchell MD, Doshi JA, Agarwal RK, Williams K, Brennan PJ. Estimating the Proportion of Healthcare-Associated Infections That Are Reasonably Preventable and the Related Mortality and Costs. Infect Control Hosp Epidemiol 2011;32:14.
167. Kassakian SZ, Mermel LA, Jefferson JA, Parenteau SL, Machan JT. Impact of Chlorhexidine Bathing on Hospital-Acquired Infections among General Medical Patients. Infect Control Hosp Epidemiol 2011;32:6.
168. Pereira BJ, Shapiro L, King AJ, Falagas ME, Strom JA, Dinarello CA. Plasma levels of IL-1 beta, TNF alpha and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. Kidney Int 1994;45:890-6.
169. Zeltzer E, Bernheim J, Korzets Z, et al. Diminished chemokine and cytokine-induced adhesion of CD4+ T cells to extracellular matrix ligands in patients with end-stage renal failure. Isr Med Assoc J 2000;2:282-6.
170. Anandh U, Bastani B, Ballal S. Granulocyte-macrophage colony-stimulating factor as an adjuvant to hepatitis B vaccination in maintenance hemodialysis patients. Am J Nephrol 2000;20:53-6.
171. Jha R, Lakhtakia S, Jaleel MA, Narayan G, Hemlatha K. Granulocyte macrophage colony stimulating factor (GM-CSF) induced sero-protection in end stage renal failure patients to hepatitis B in vaccine non-responders. Ren Fail 2001;23:629-36.
172. Fabrizi F, Ganeshan SV, Dixit V, Martin P. Meta-analysis: the adjuvant role of granulocyte macrophage-colony stimulating factor on immunological response to hepatitis B virus vaccine in end-stage renal disease. Aliment Pharmacol Ther 2006;24:789-96.
173. Singh NP, Mandal SK, Thakur A, et al. Efficacy of GM-CSF as an adjuvant to hepatitis B vaccination in patients with chronic renal failure--results of a prospective, randomized trial. Ren Fail 2003;25:255-66.
174. Sudhagar K, Chandrasekar S, Rao MS, Ravichandran R. Effect of granulocyte macrophage colony stimulating factor on hepatitis-B vaccination in haemodialysis patients. J Assoc Physicians India 1999;47:602-4.